

12

1 / 31

FIG. 1

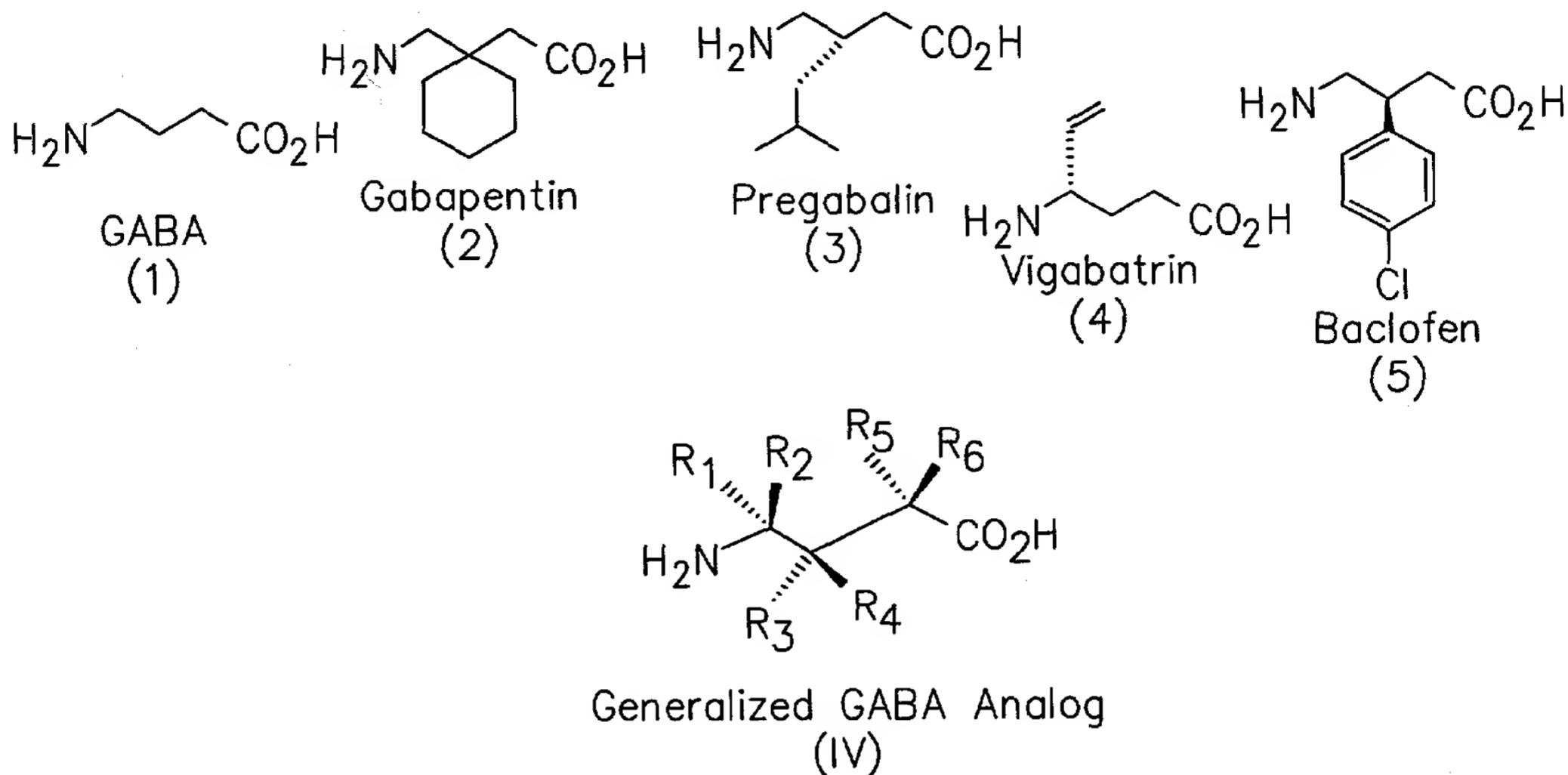
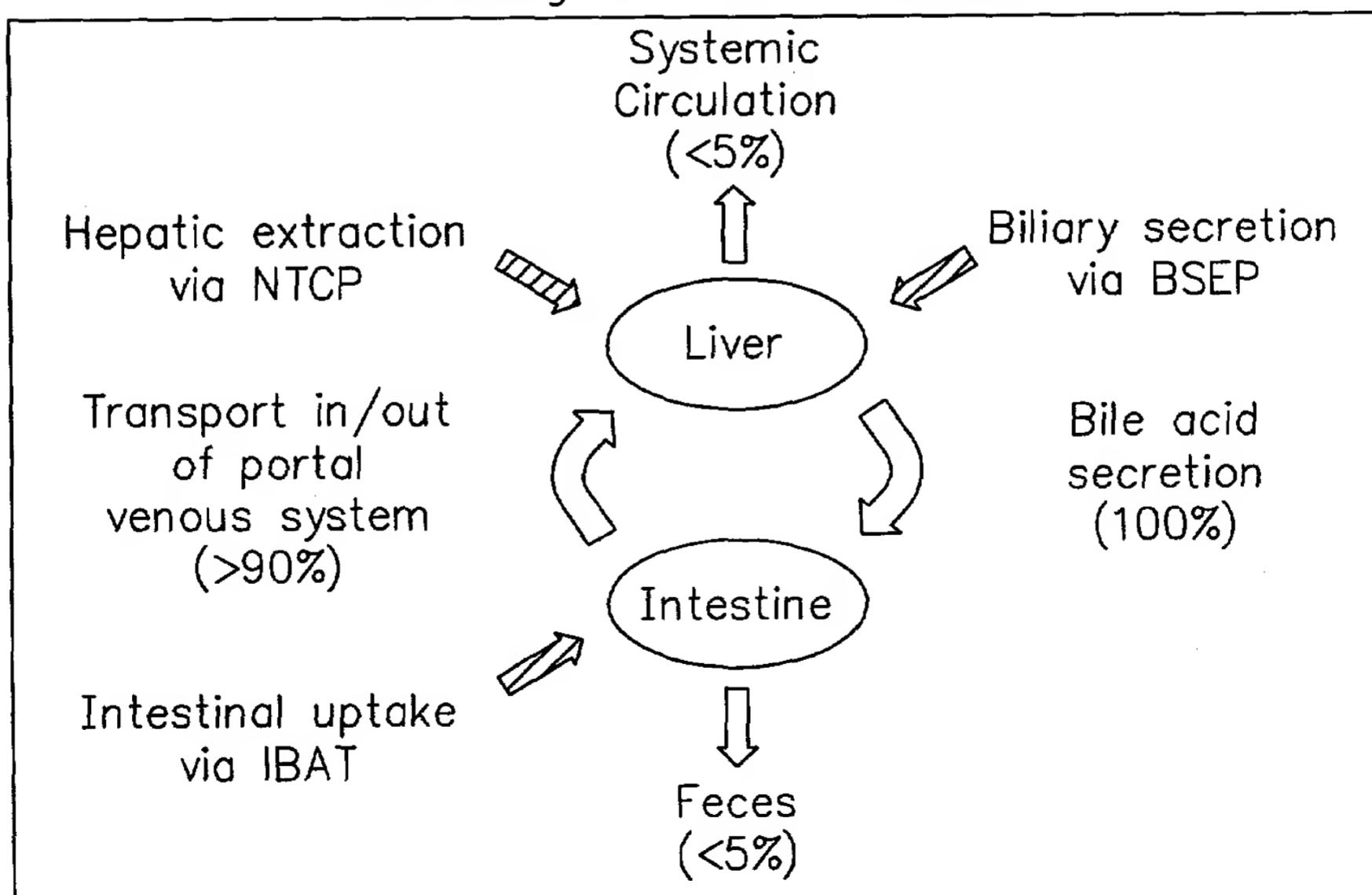


FIG. 2

## The Enterohepatic Circulation with Key Transporter Proteins Mediating Bile Acid Circulation



2/31

**FIG. 3**

*Bile Acid Conjugates of HMG-CoA Reductase Inhibitor*

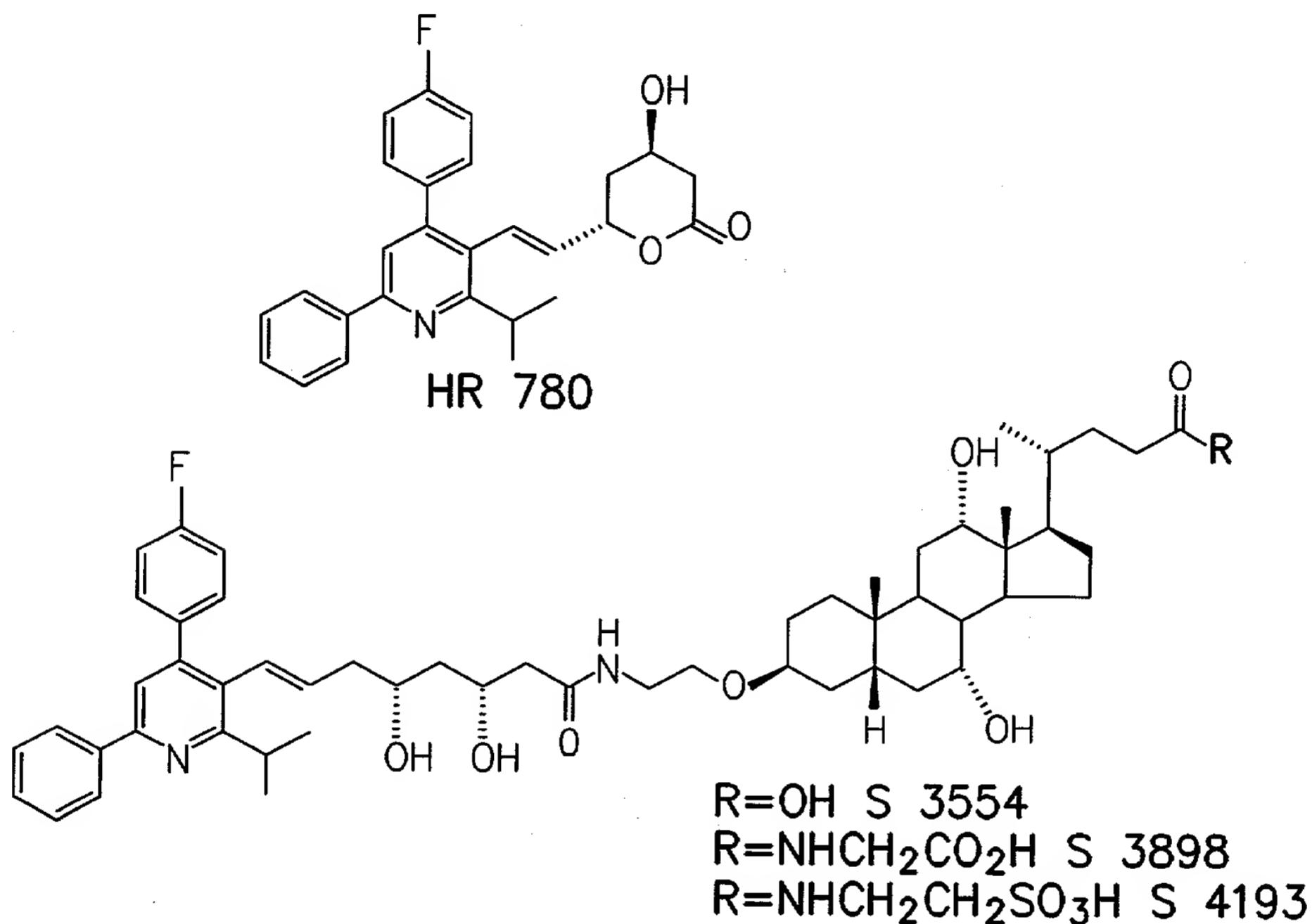
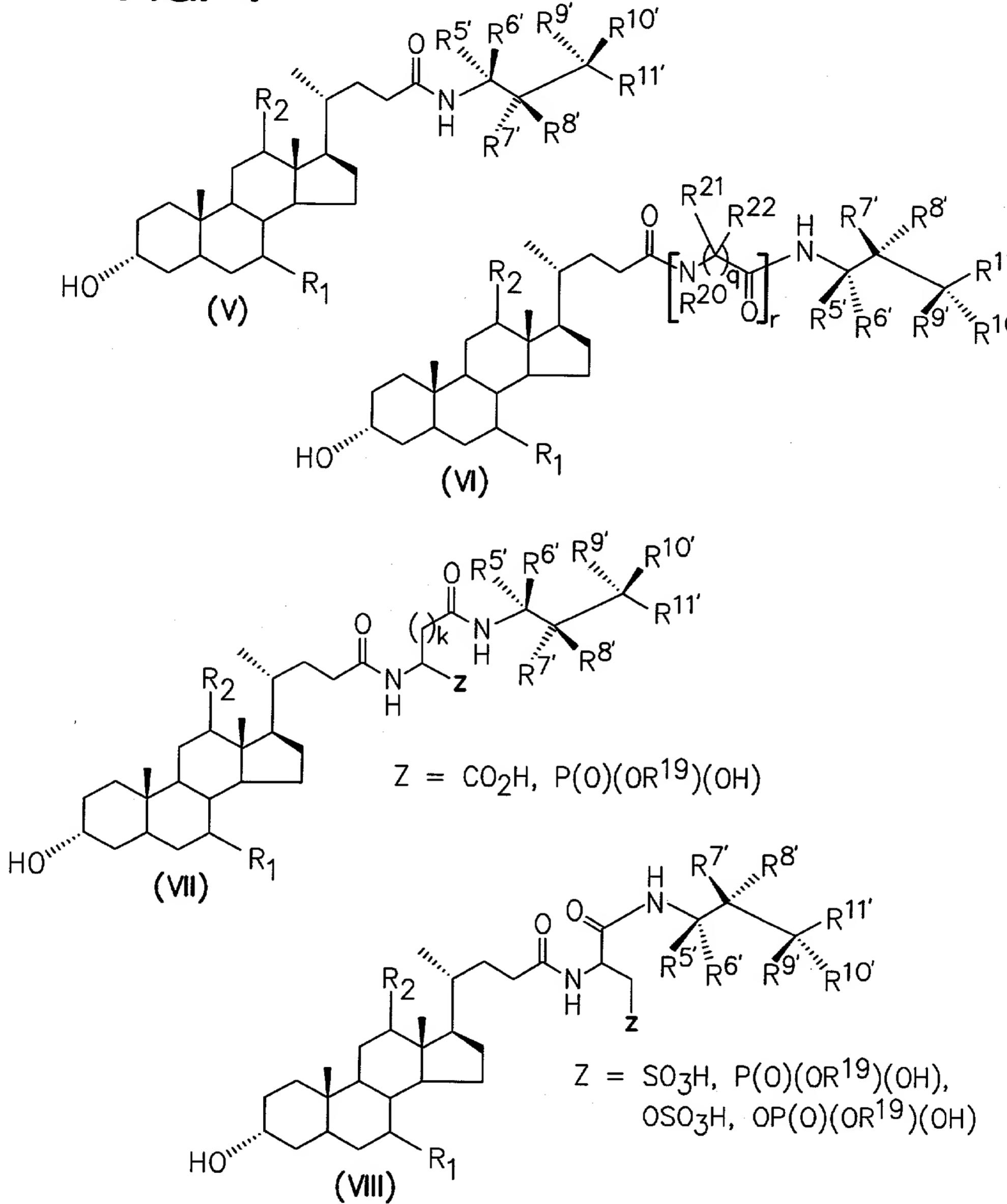


FIG. 4

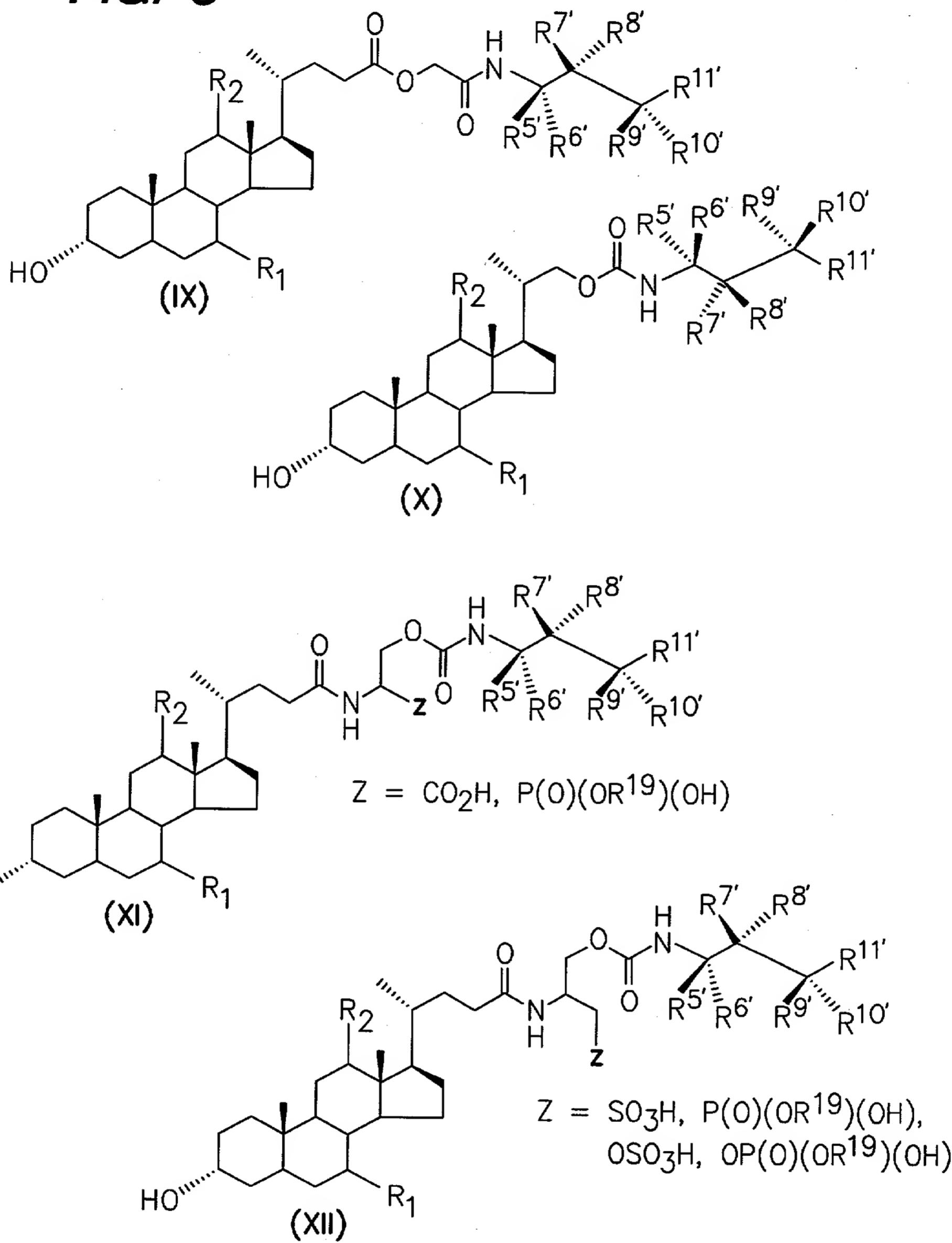
3/31



R<sub>1</sub> =  $\alpha$ -OH; R<sub>2</sub> =  $\alpha$ -OH (Cholate)  
R<sub>1</sub> =  $\beta$ -OH; R<sub>2</sub> = H (Ursodeoxycholate)  
R<sub>1</sub> =  $\alpha$ -OH; R<sub>2</sub> = H (Chenodeoxycholate)  
R<sub>1</sub> = H; R<sub>2</sub> =  $\alpha$ -OH (Deoxycholate)  
R<sub>1</sub> =  $\beta$ -OH; R<sub>2</sub> =  $\alpha$ -OH (Ursocholate)  
R<sub>1</sub> = H; R<sub>2</sub> = H (Lithocholate)

FIG. 5

4/31



R1 =  $\alpha$ -OH; R2 =  $\alpha$ -OH (Cholate)

R1 =  $\beta$ -OH; R2 = H (Ursodeoxycholate)

R1 =  $\alpha$ -OH; R2 = H (Chenodeoxycholate)

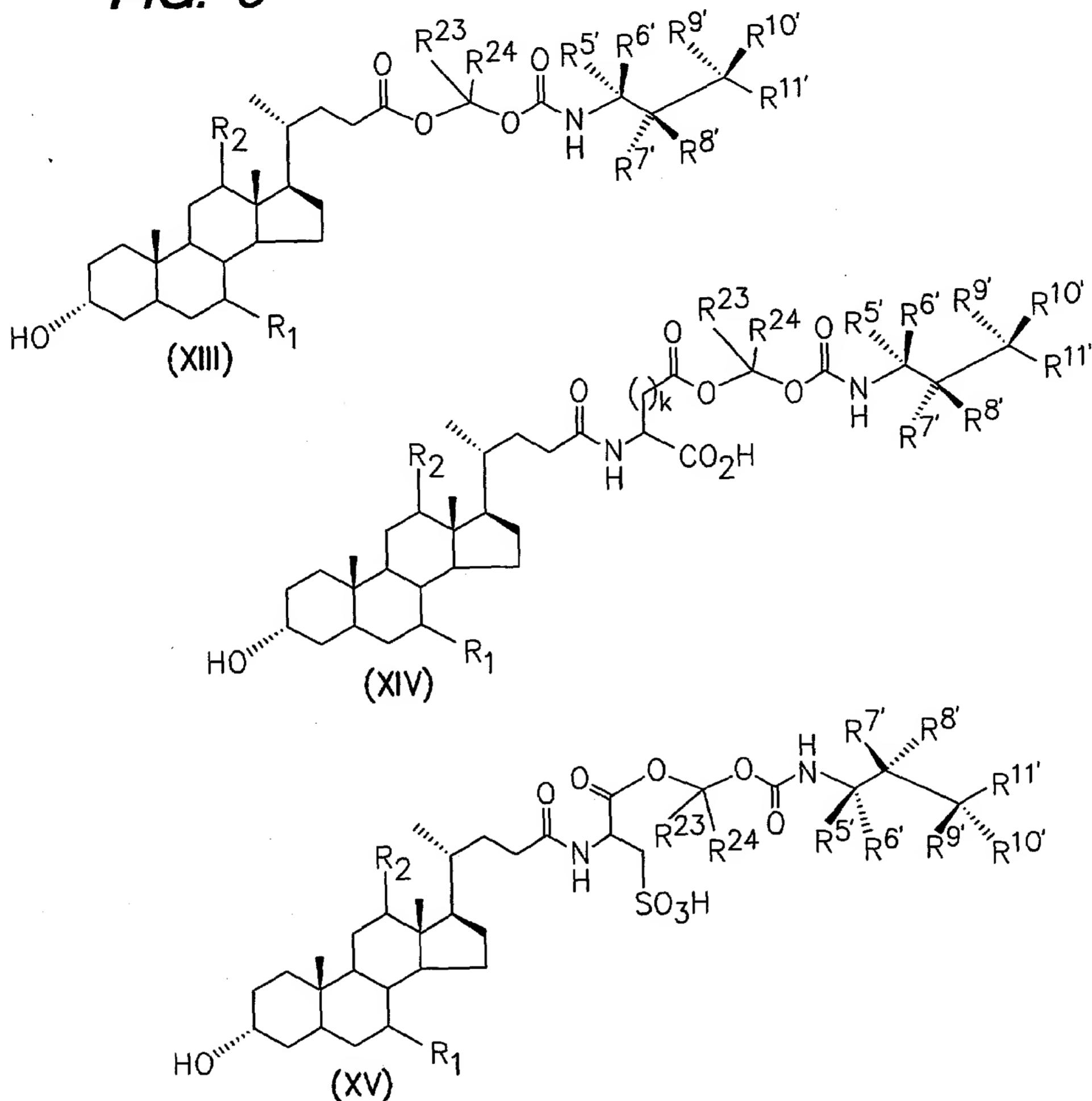
R1 = H; R2 =  $\alpha$ -OH (Deoxycholate)

R1 =  $\beta$ -OH; R2 =  $\alpha$ -OH (Ursocholate)

R1 = H; R2 = H (Lithocholate)

5/31

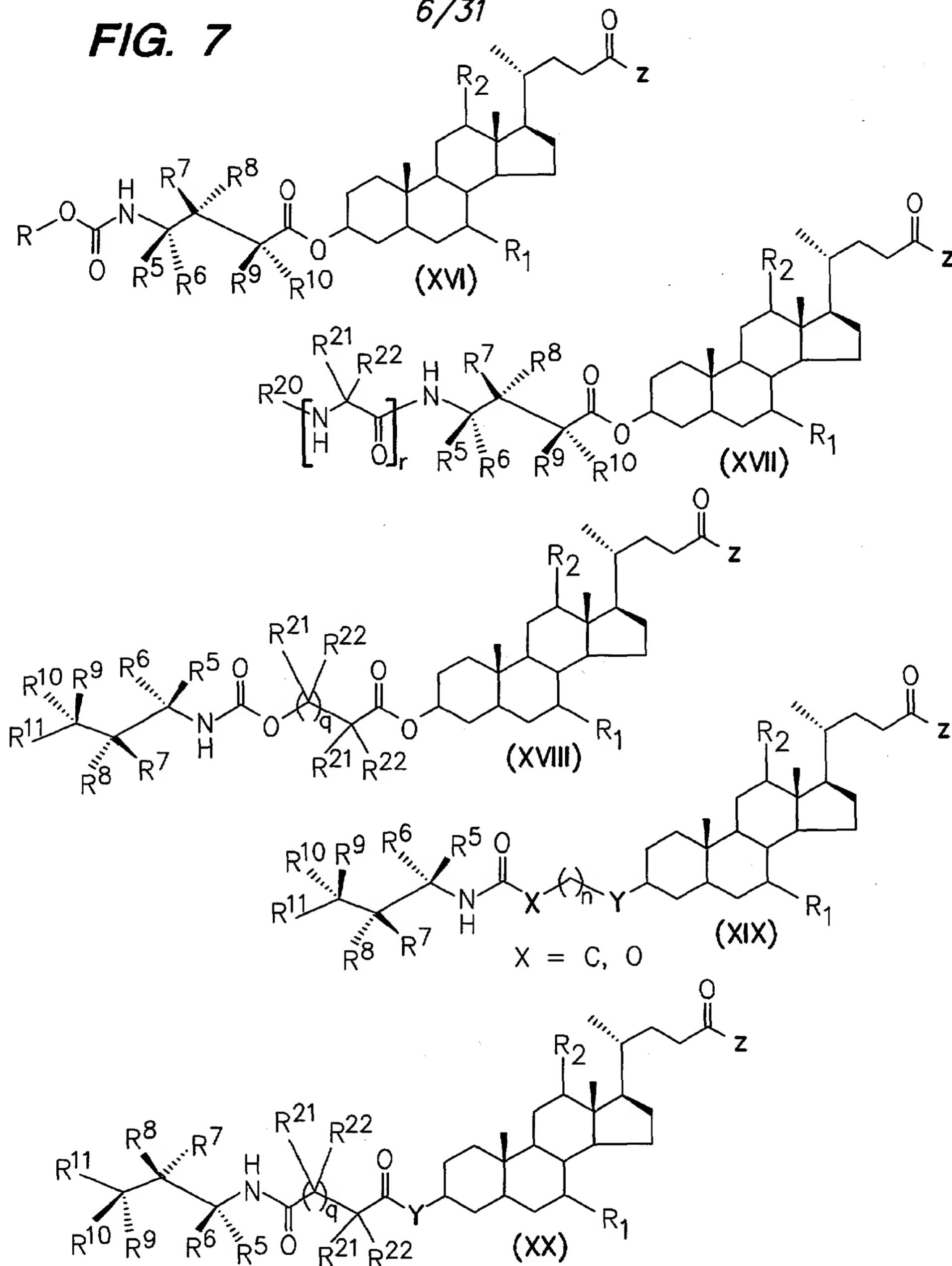
FIG. 6



R<sub>1</sub> =  $\alpha$ -OH; R<sub>2</sub> =  $\alpha$ -OH (Cholate)  
R<sub>1</sub> =  $\beta$ -OH; R<sub>2</sub> = H (Ursodeoxycholate)  
R<sub>1</sub> =  $\alpha$ -OH; R<sub>2</sub> = H (Chenodeoxycholate)  
R<sub>1</sub> = H; R<sub>2</sub> =  $\alpha$ -OH (Deoxycholate)  
R<sub>1</sub> =  $\beta$ -OH; R<sub>2</sub> =  $\alpha$ -OH (Ursocholate)  
R<sub>1</sub> = H; R<sub>2</sub> = H (Lithocholate)

**FIG. 7**

6/31

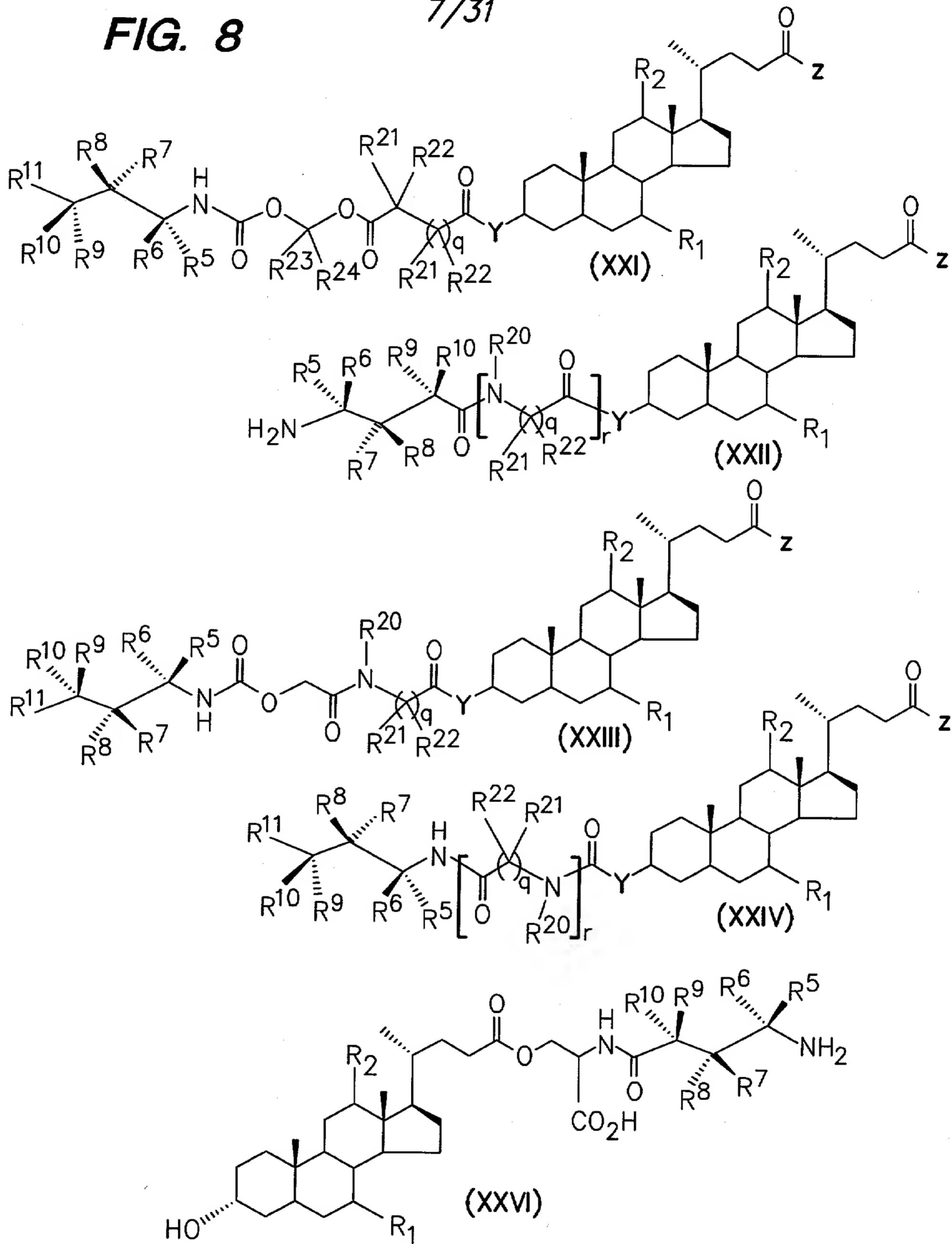


R<sub>1</sub> =  $\alpha$ -OH; R<sub>2</sub> =  $\alpha$ -OH (Cholate)  
 R<sub>1</sub> =  $\beta$ -OH; R<sub>2</sub> = H (Ursodeoxycholate)  
 R<sub>1</sub> =  $\alpha$ -OH; R<sub>2</sub> = H (Chenodeoxycholate)  
 R<sub>1</sub> = H; R<sub>2</sub> =  $\alpha$ -OH (Deoxycholate)  
 R<sub>1</sub> =  $\beta$ -OH; R<sub>2</sub> =  $\alpha$ -OH (Ursocholate)  
 R<sub>1</sub> = H; R<sub>2</sub> = H (Lithocholate)

Y =  $\alpha$ -O      Z = OH  
 Y =  $\beta$ -O      Z = N  
 Y =  $\alpha$ -NH      CO<sub>2</sub>H  
 Y =  $\beta$ -NH      SO<sub>3</sub>H

FIG. 8

7/31

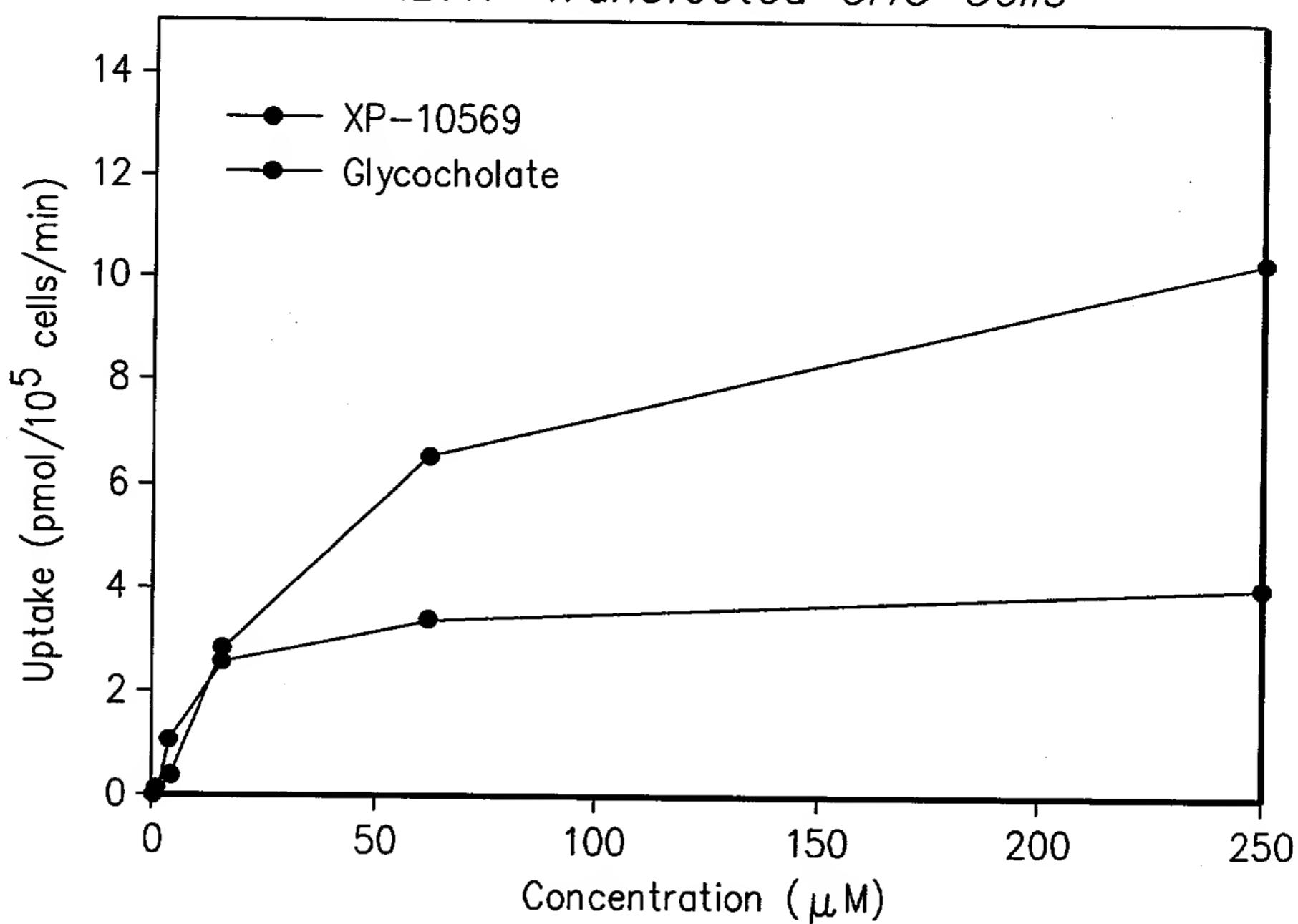


$R_1 = \alpha\text{-OH}; R_2 = \alpha\text{-OH}$  (Cholate)  
 $R_1 = \beta\text{-OH}; R_2 = \text{H}$  (Ursodeoxycholate)  
 $R_1 = \alpha\text{-OH}; R_2 = \text{H}$  (Chenodeoxycholate)  
 $R_1 = \text{H}; R_2 = \alpha\text{-OH}$  (Deoxycholate)  
 $R_1 = \beta\text{-OH}; R_2 = \alpha\text{-OH}$  (Ursocholate)  
 $R_1 = \text{H}; R_2 = \text{H}$  (Lithocholate)

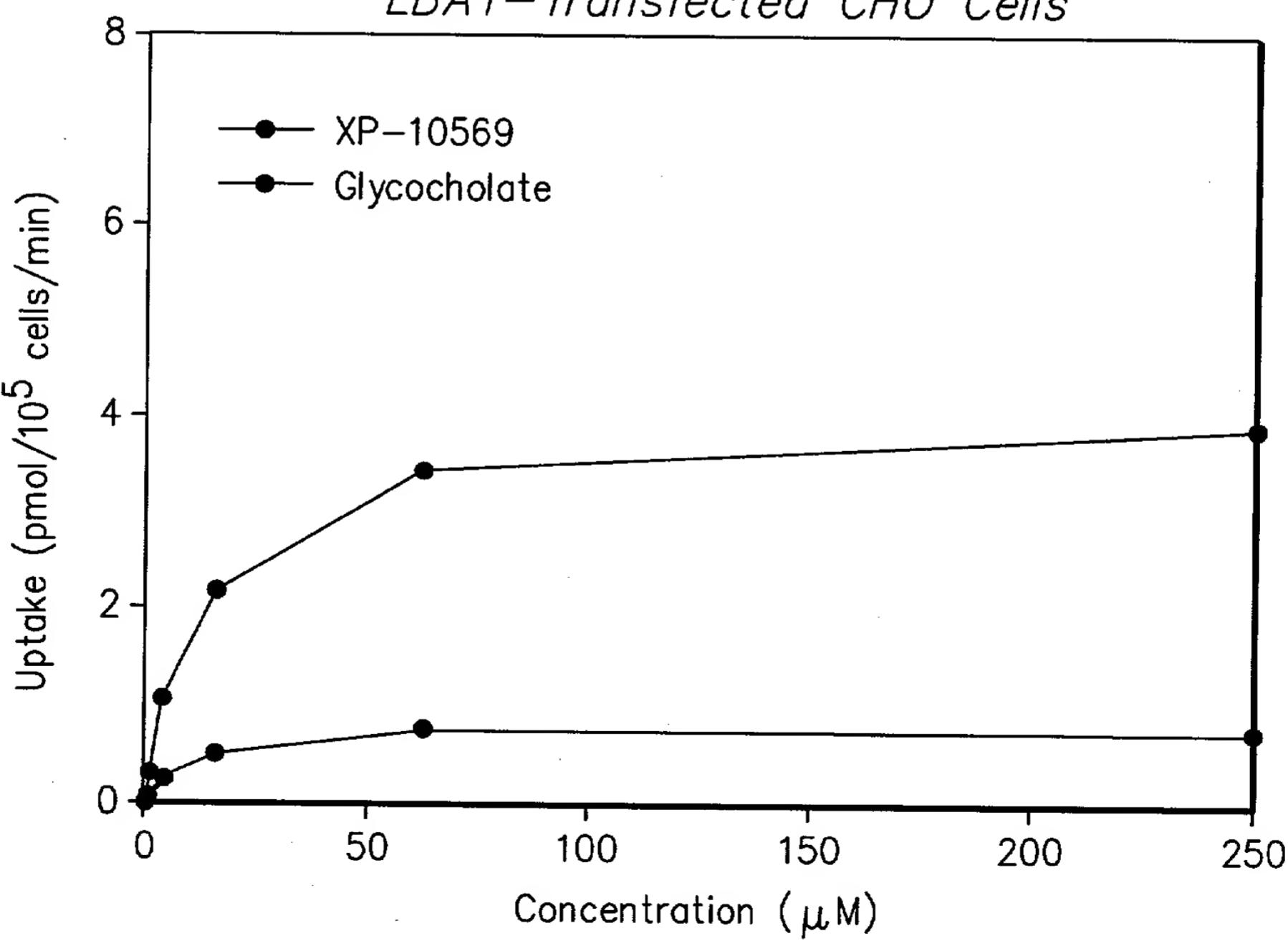
$Y = \alpha\text{-O}$        $Z = \text{OH}$   
 $Y = \beta\text{-O}$        $Z = \text{N}-\text{CH}_2\text{CO}_2\text{H}$   
 $Y = \alpha\text{-NH}$   
 $Y = \beta\text{-NH}$   
 $Z = \text{N}-\text{CH}_2\text{SO}_3\text{H}$

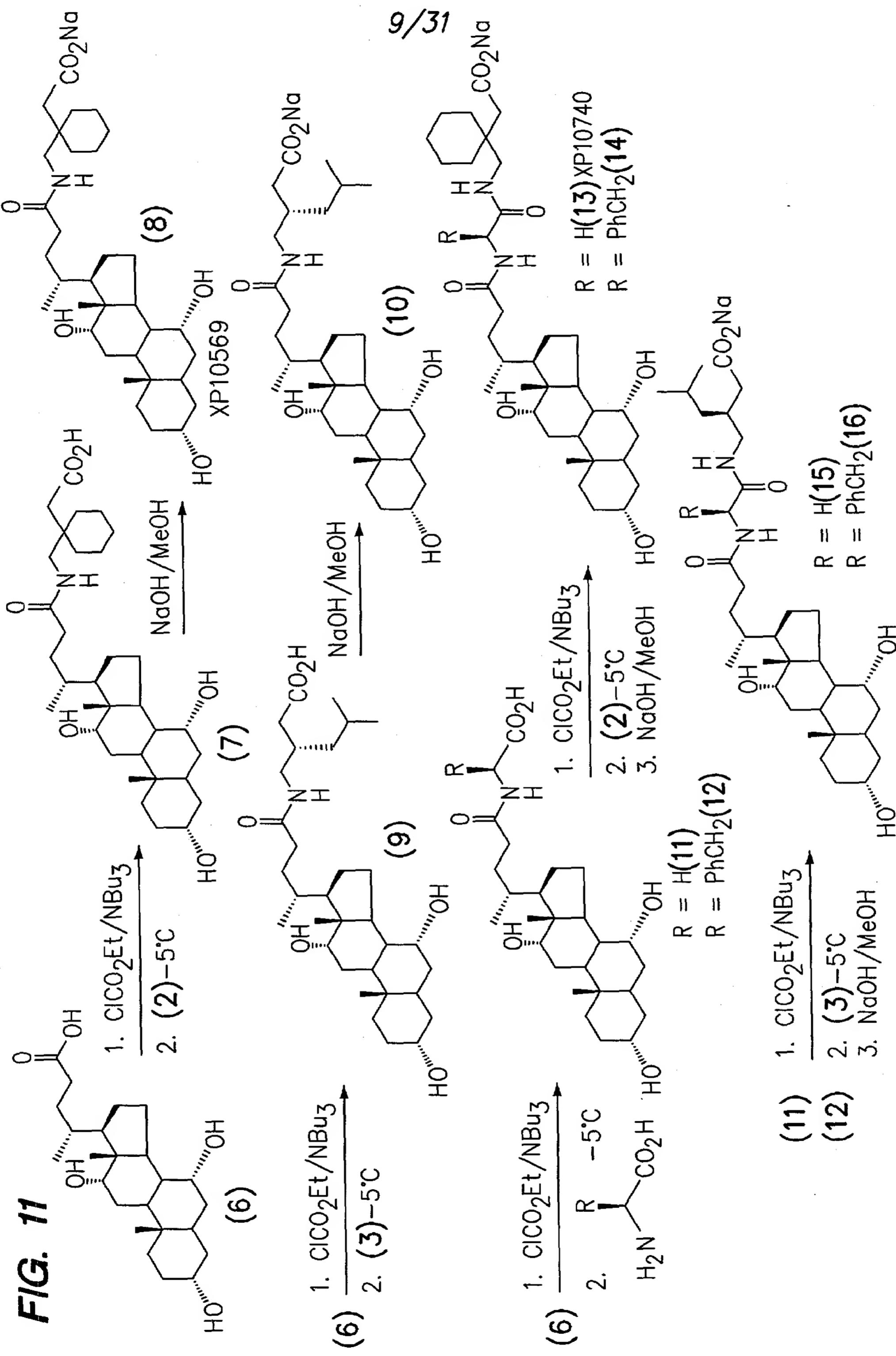
8/31

**FIG. 9** Uptake of (8) (XP10569) or Glycocholate by  
IBAT-Transfected CHO Cells



**FIG. 10** Uptake of (8) (XP10569) or Glycocholate by  
LBAT-Transfected CHO Cells





10 OF 31

10/31

FIG. 12.  $\text{O} \text{---} \text{C}_2\text{H}$

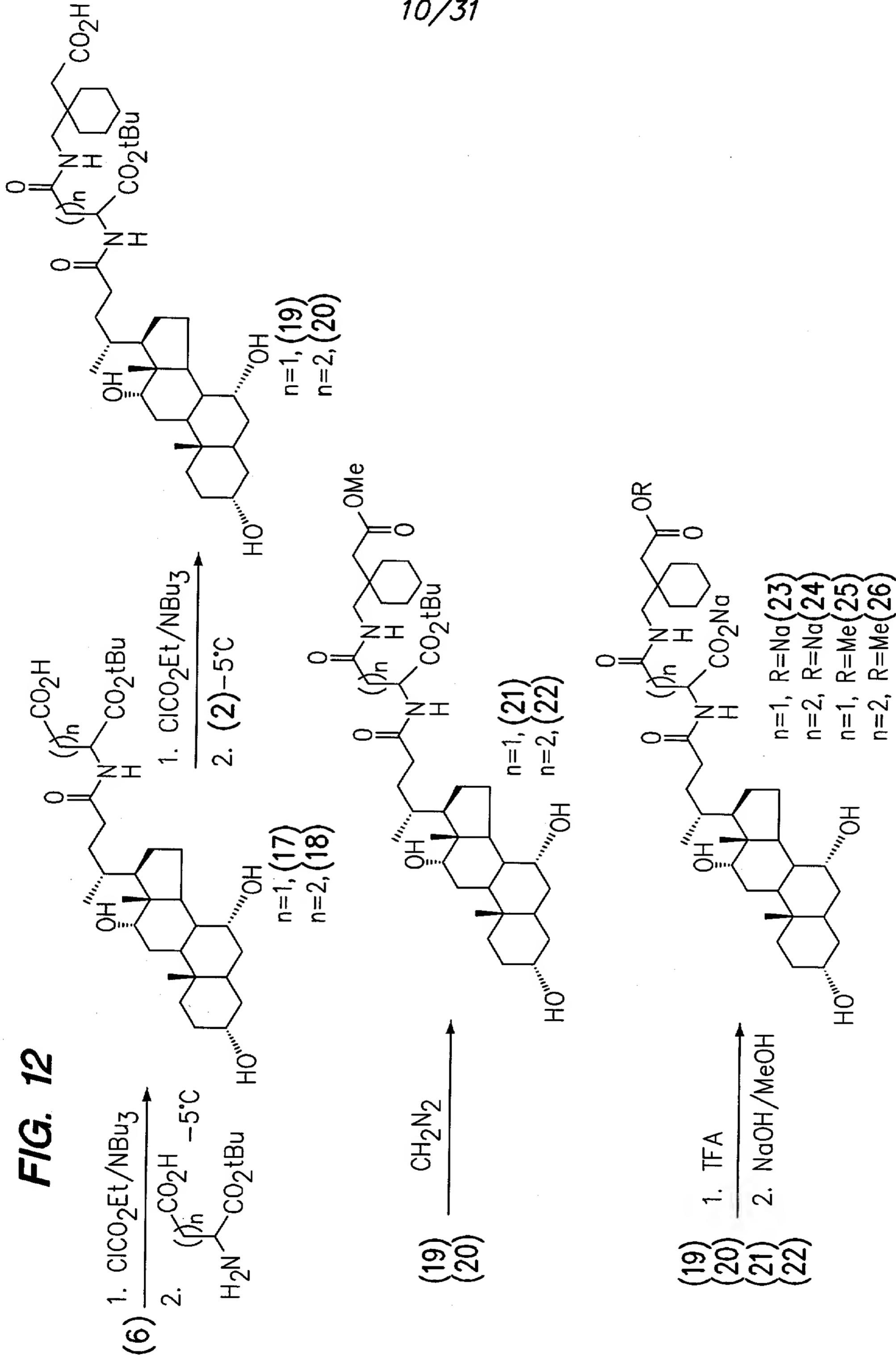
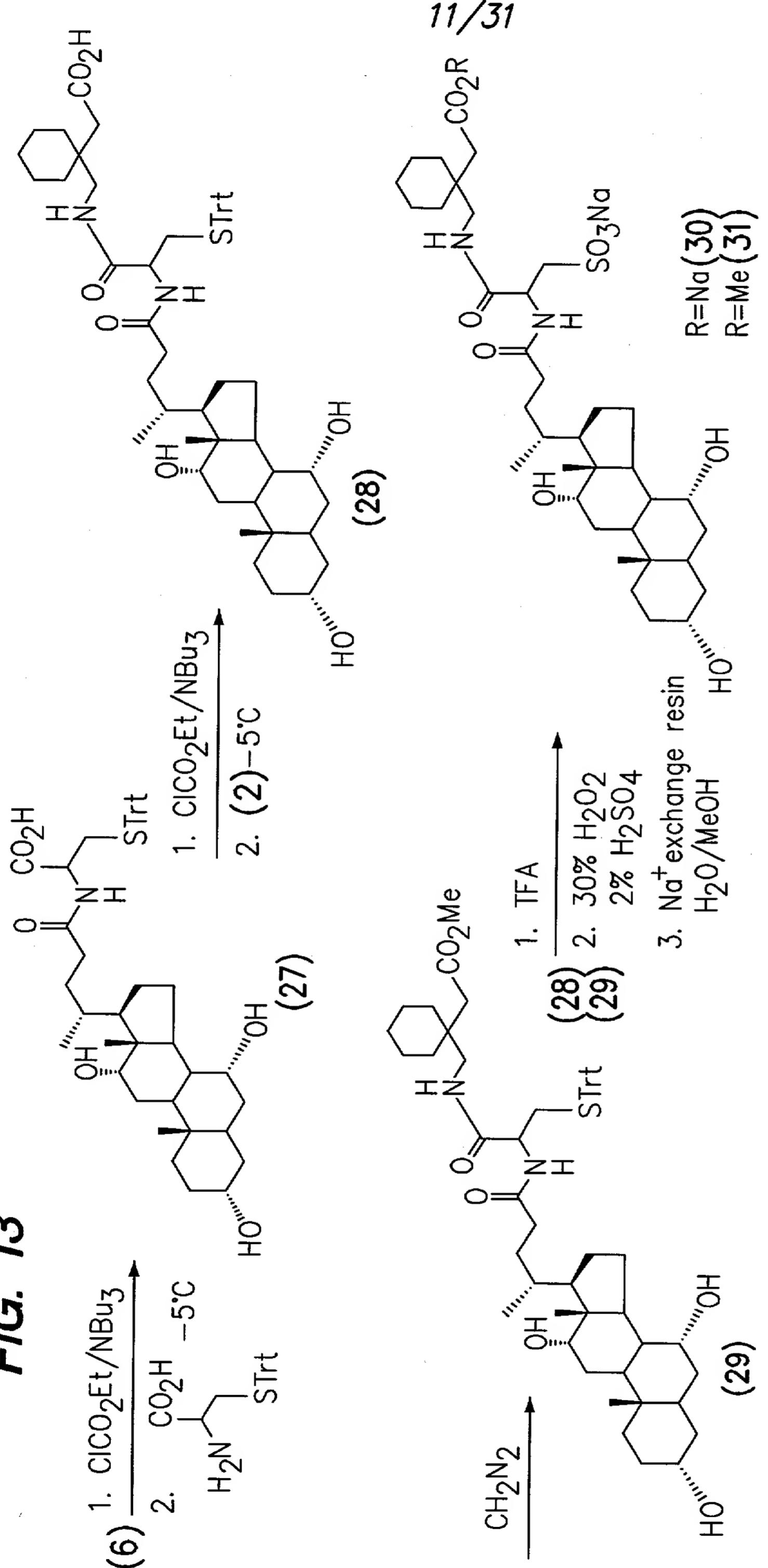
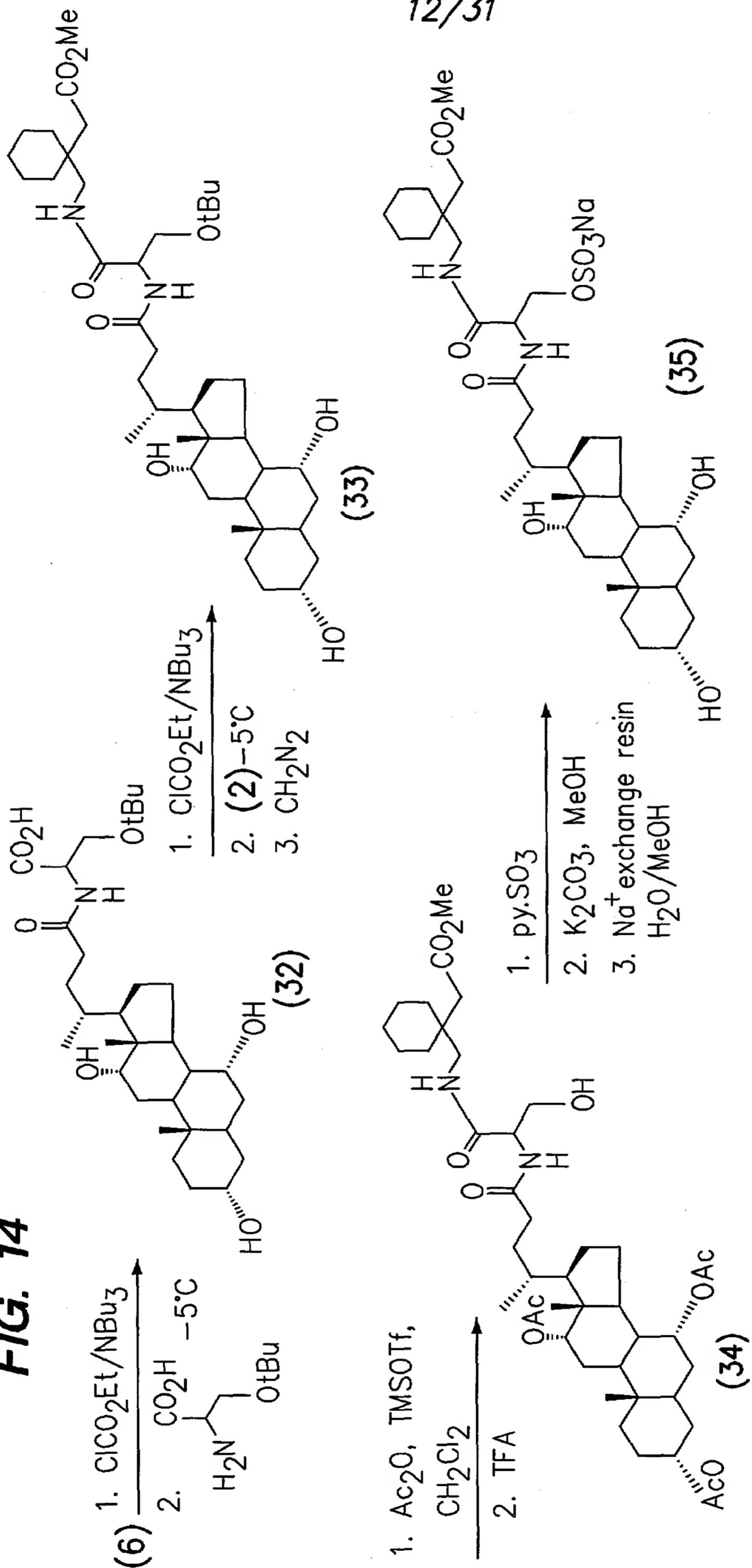


FIG. 13



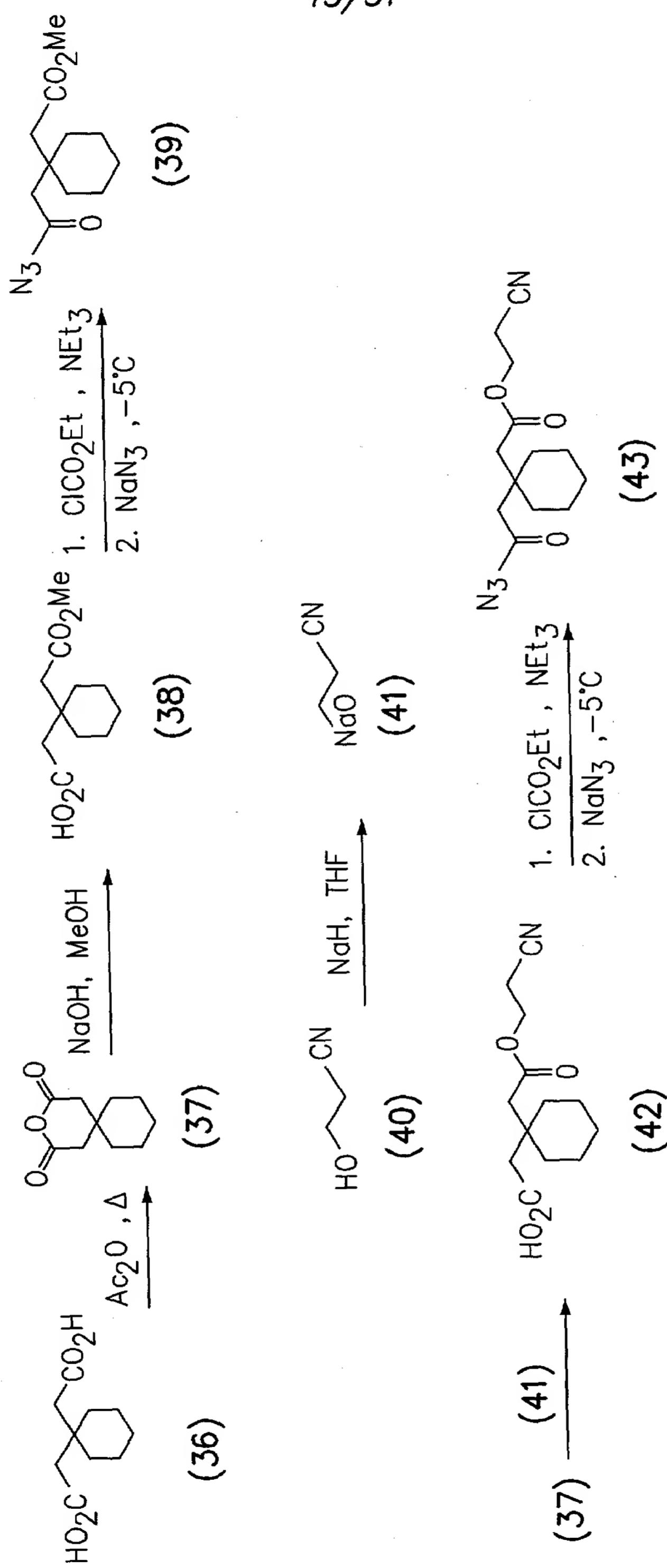
12/31

**FIG. 14**



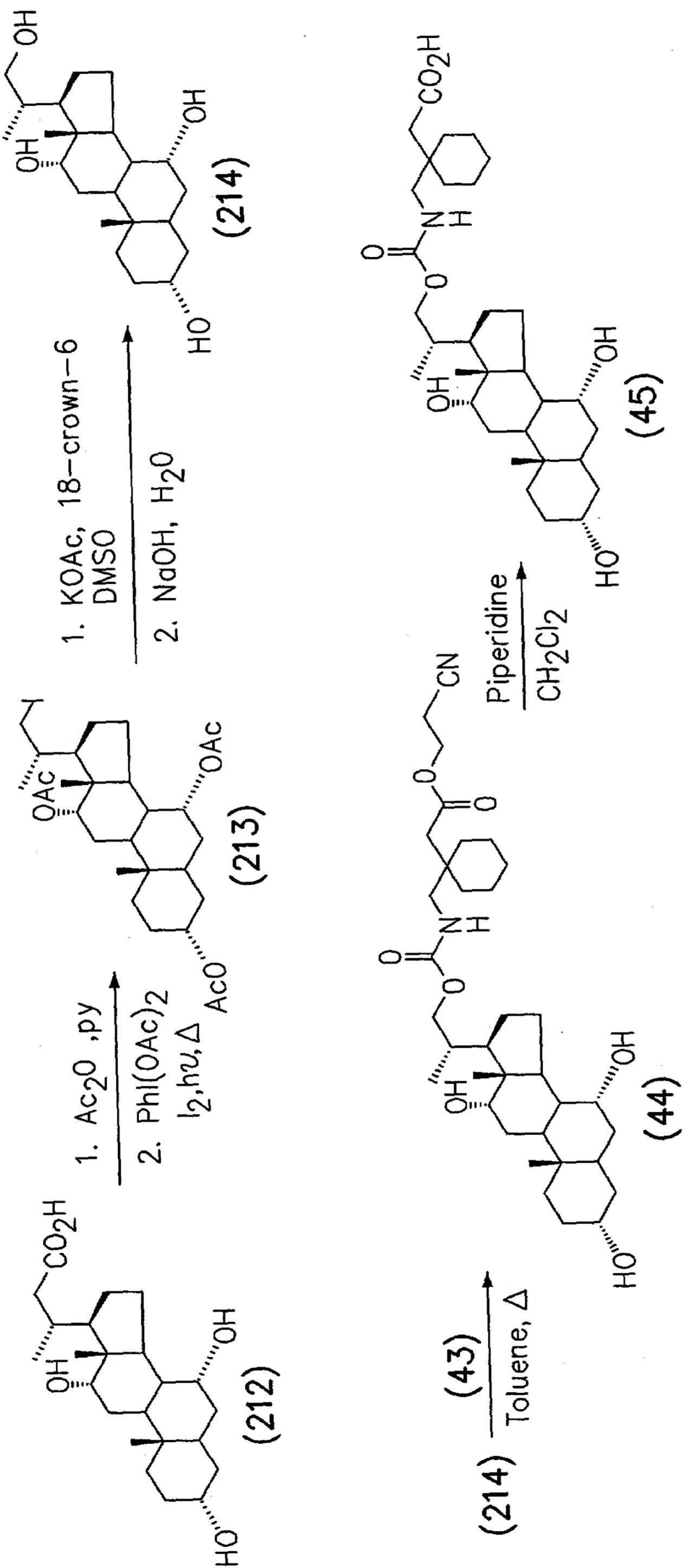
13/31

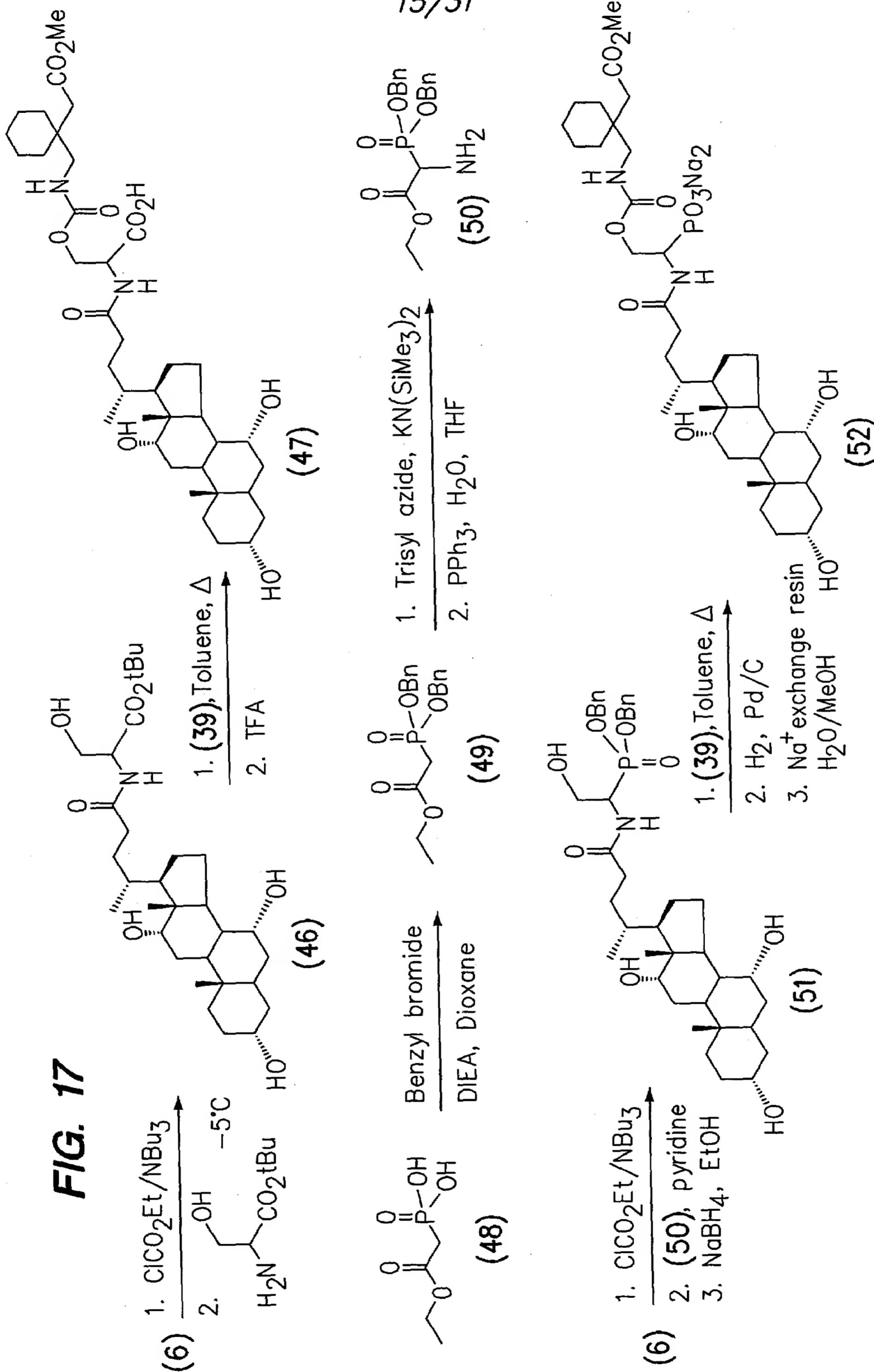
FIG. 15



14/31

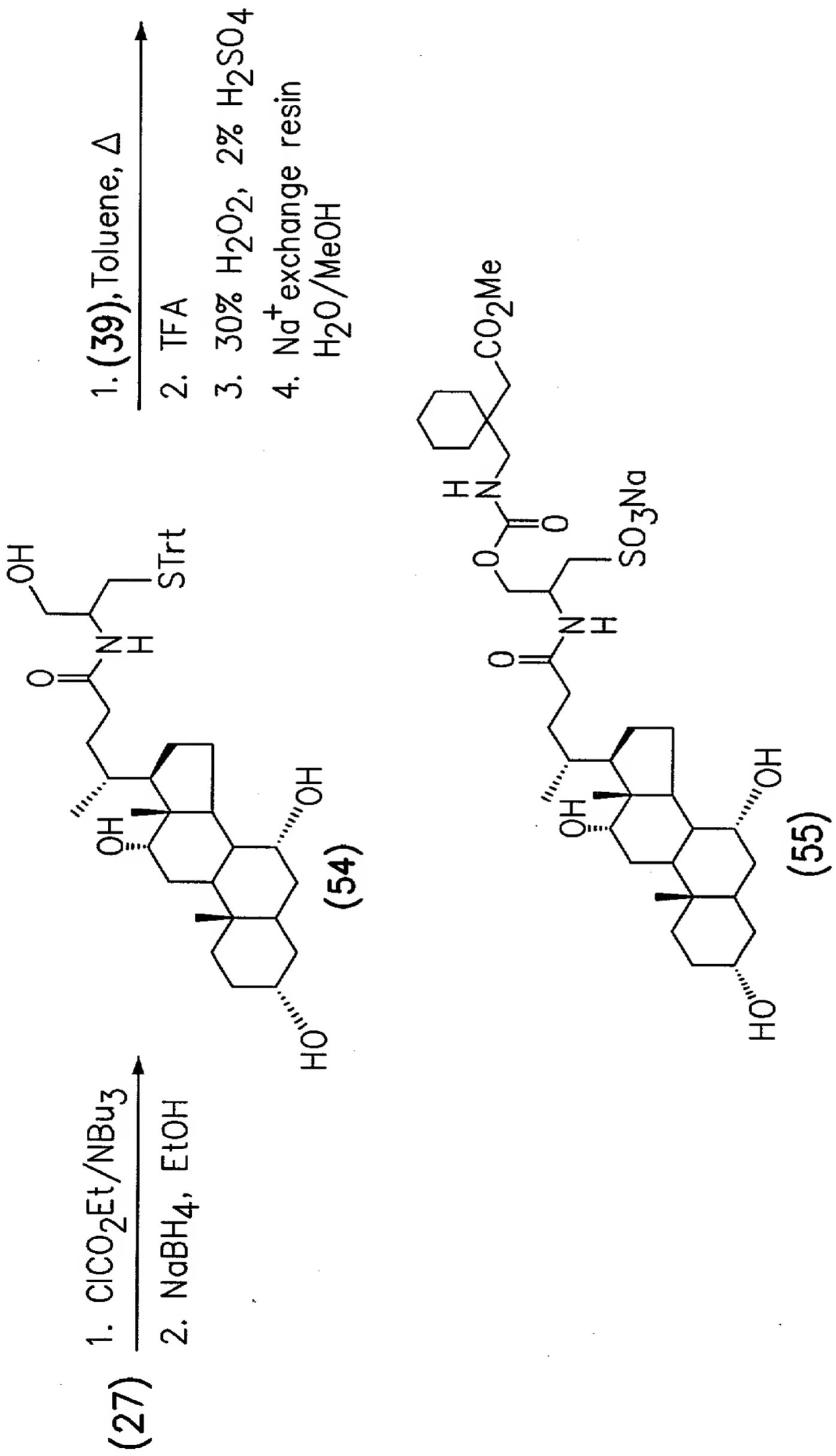
FIG. 16





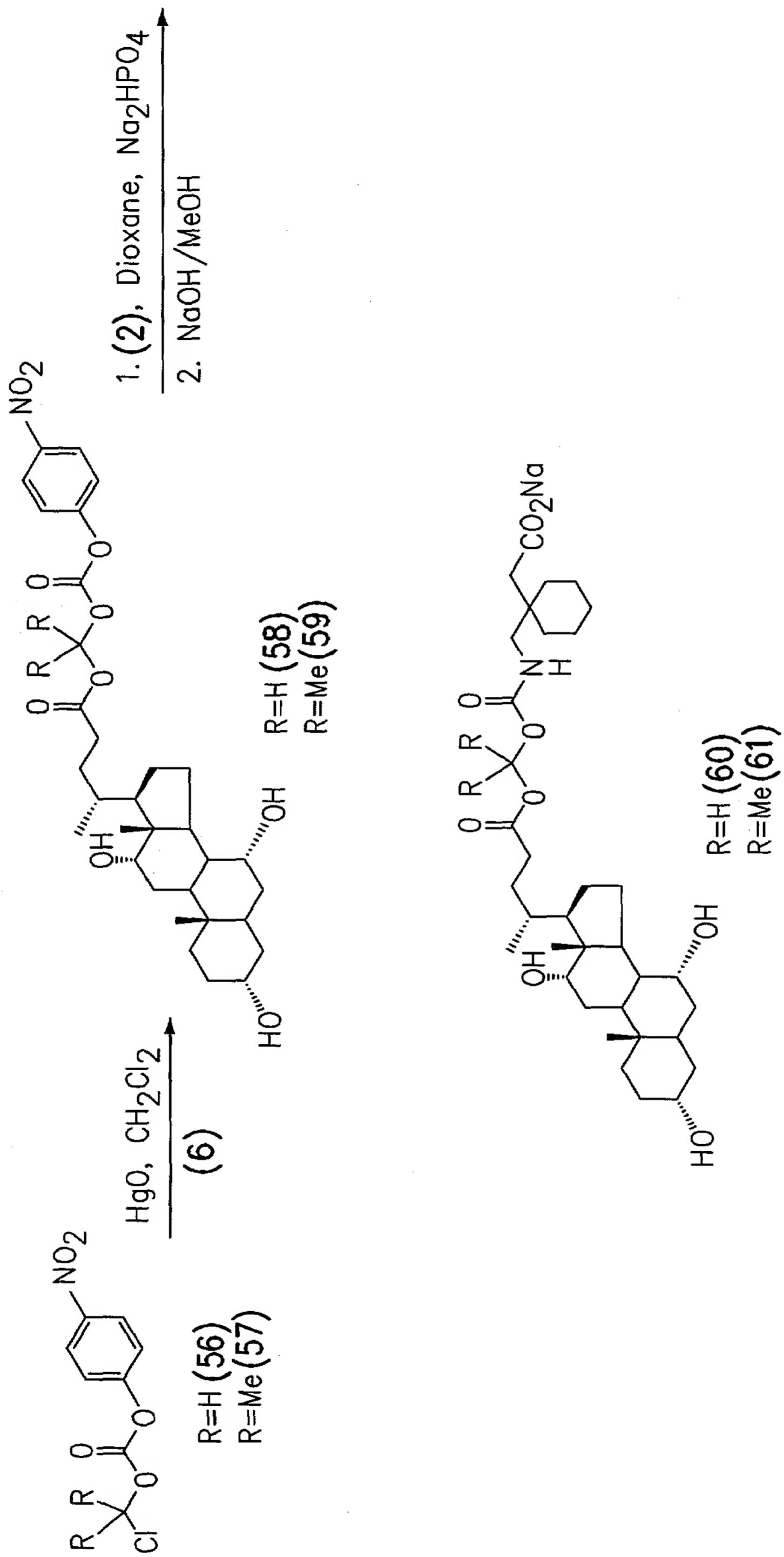
16/31

FIG. 18

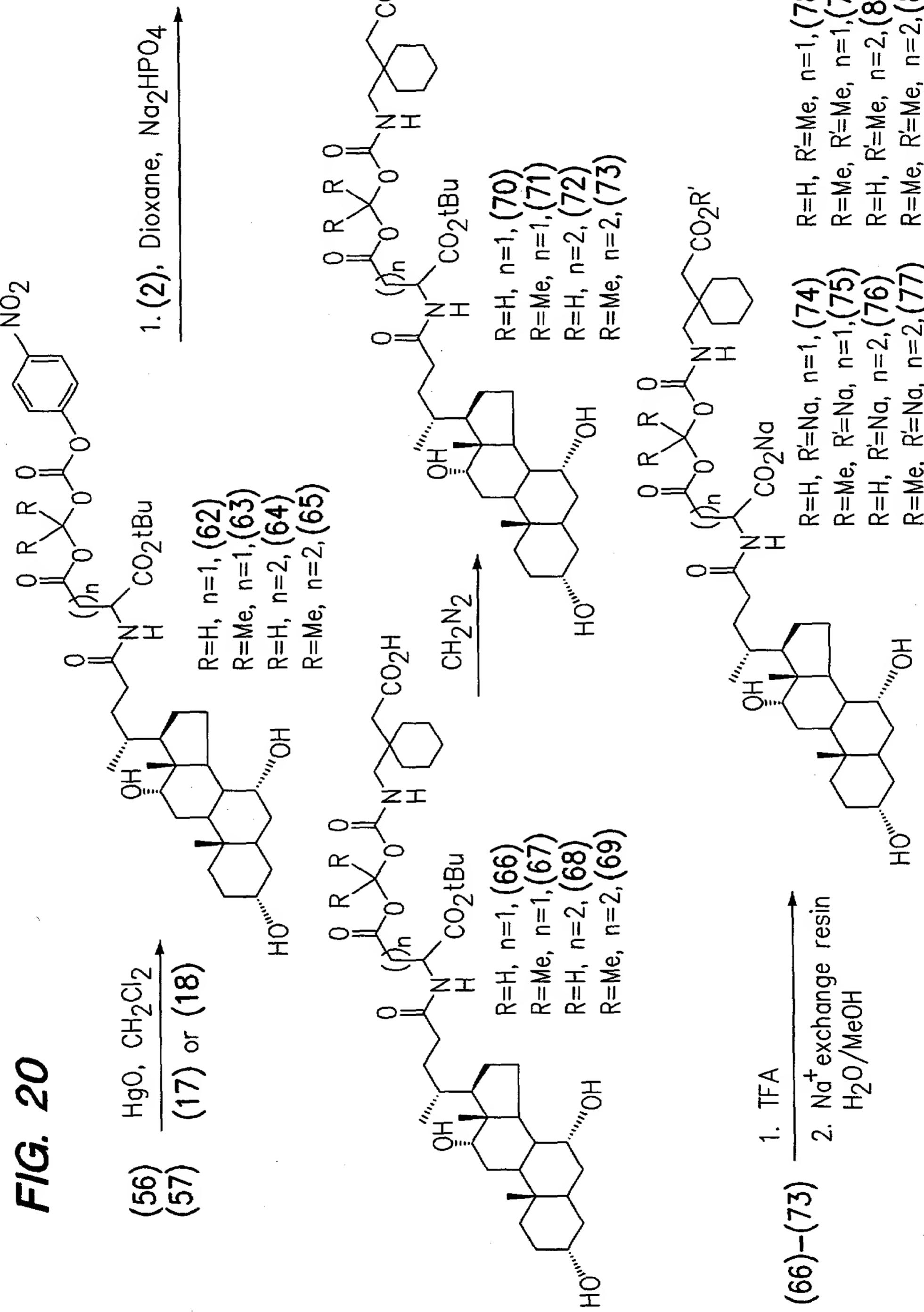


17/31

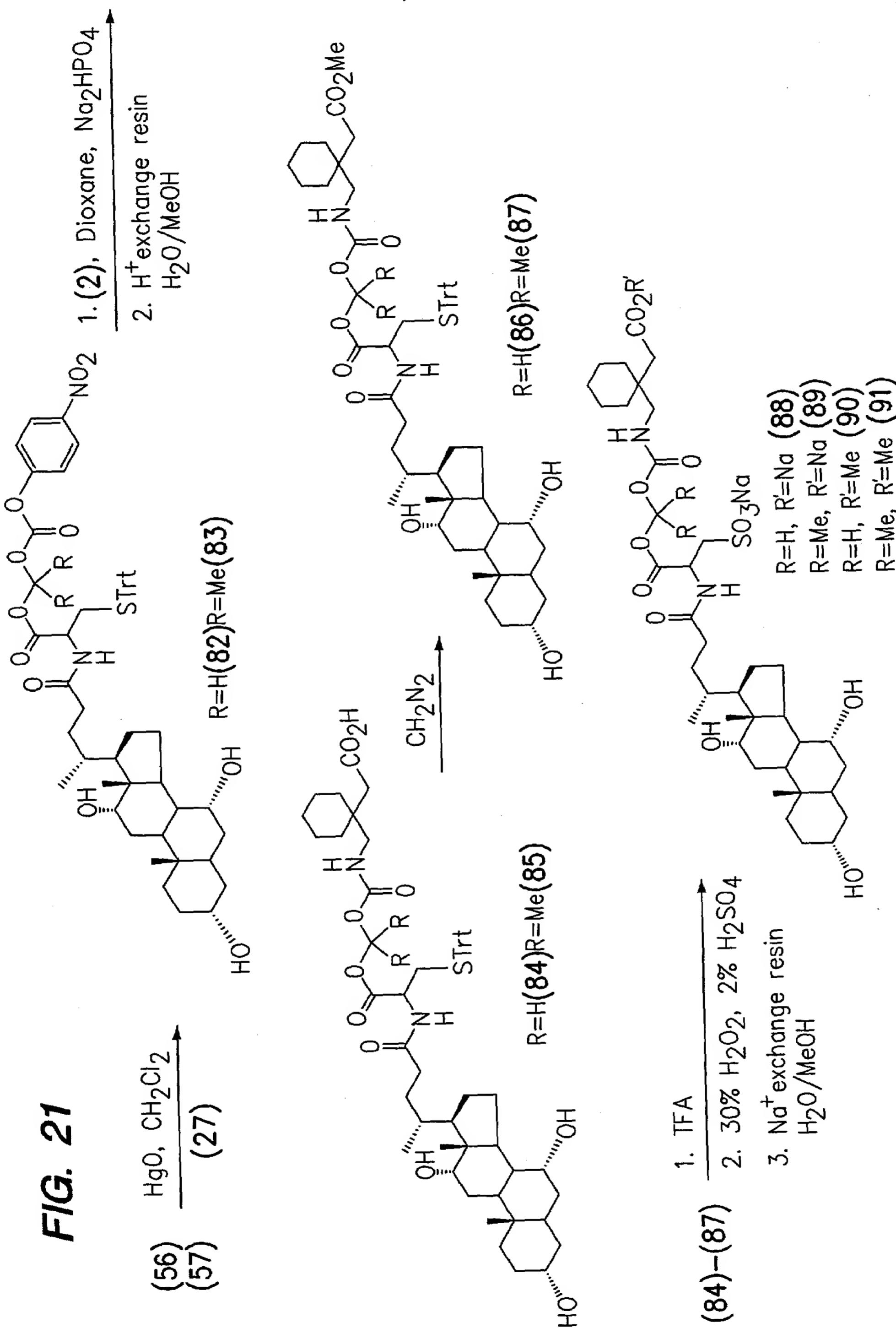
FIG. 19



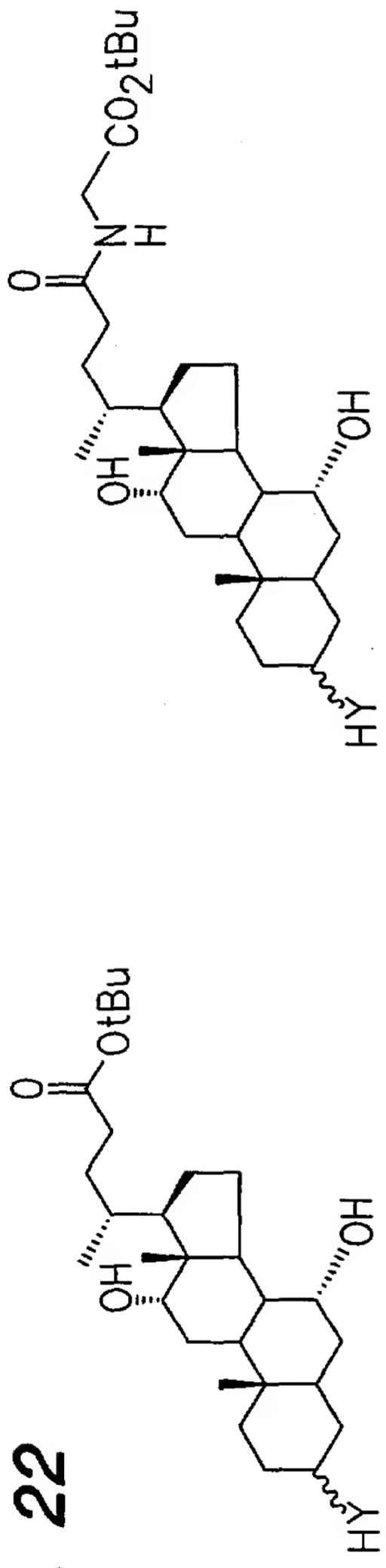
18/31



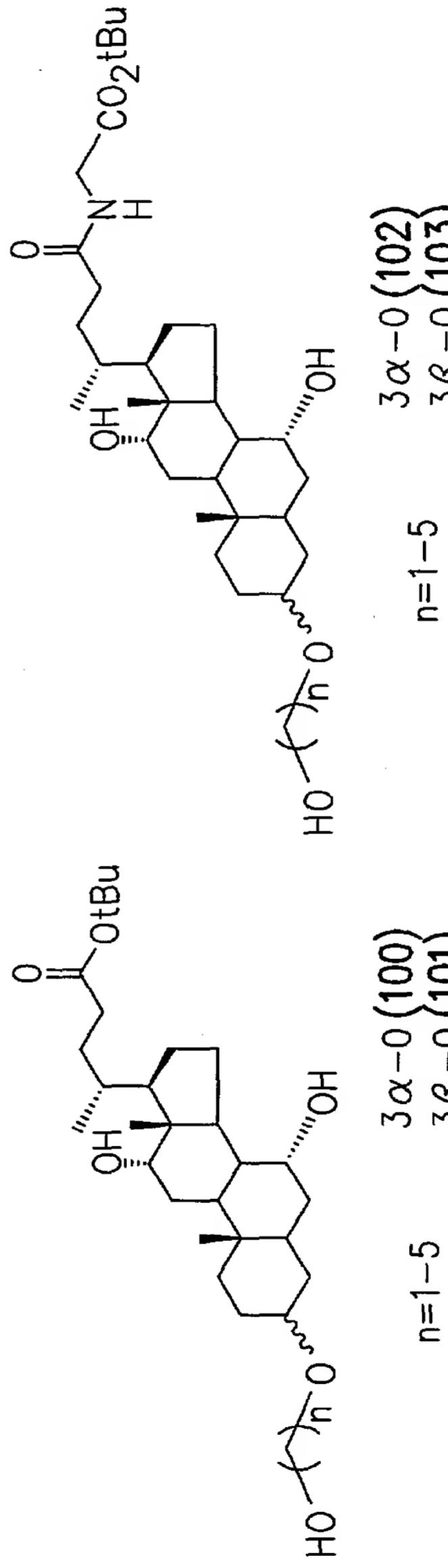
19/31



20/31



$\gamma = 3\alpha - O (92)$   
 $\gamma = 3\beta - O (93)$   
 $\gamma = 3\alpha - NH (94)$   
 $\gamma = 3\beta - NH (95)$



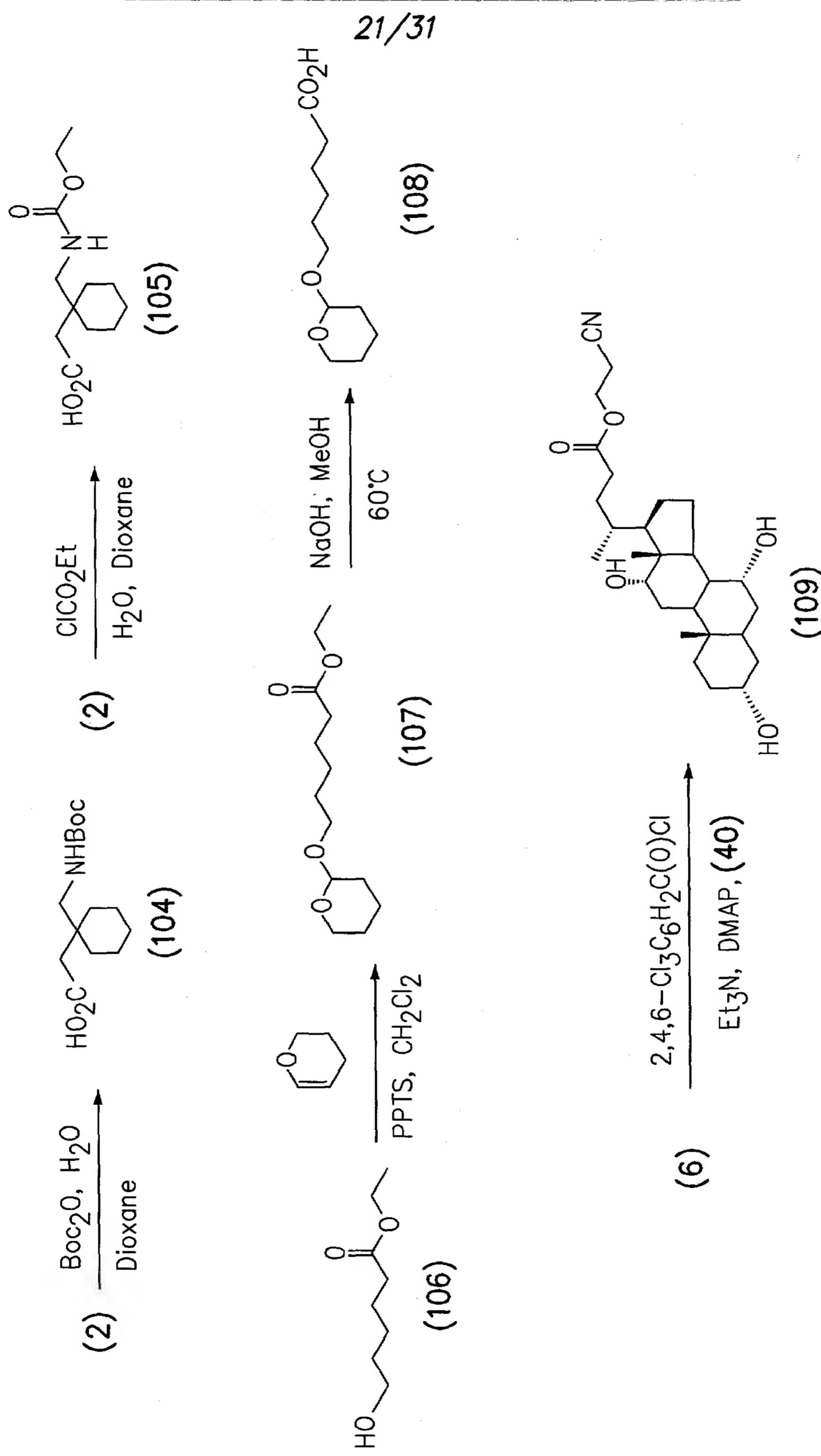
$3\alpha - O (100)$   
 $3\beta - O (101)$

$n = 1 - 5$

$3\alpha - O (102)$   
 $3\beta - O (103)$

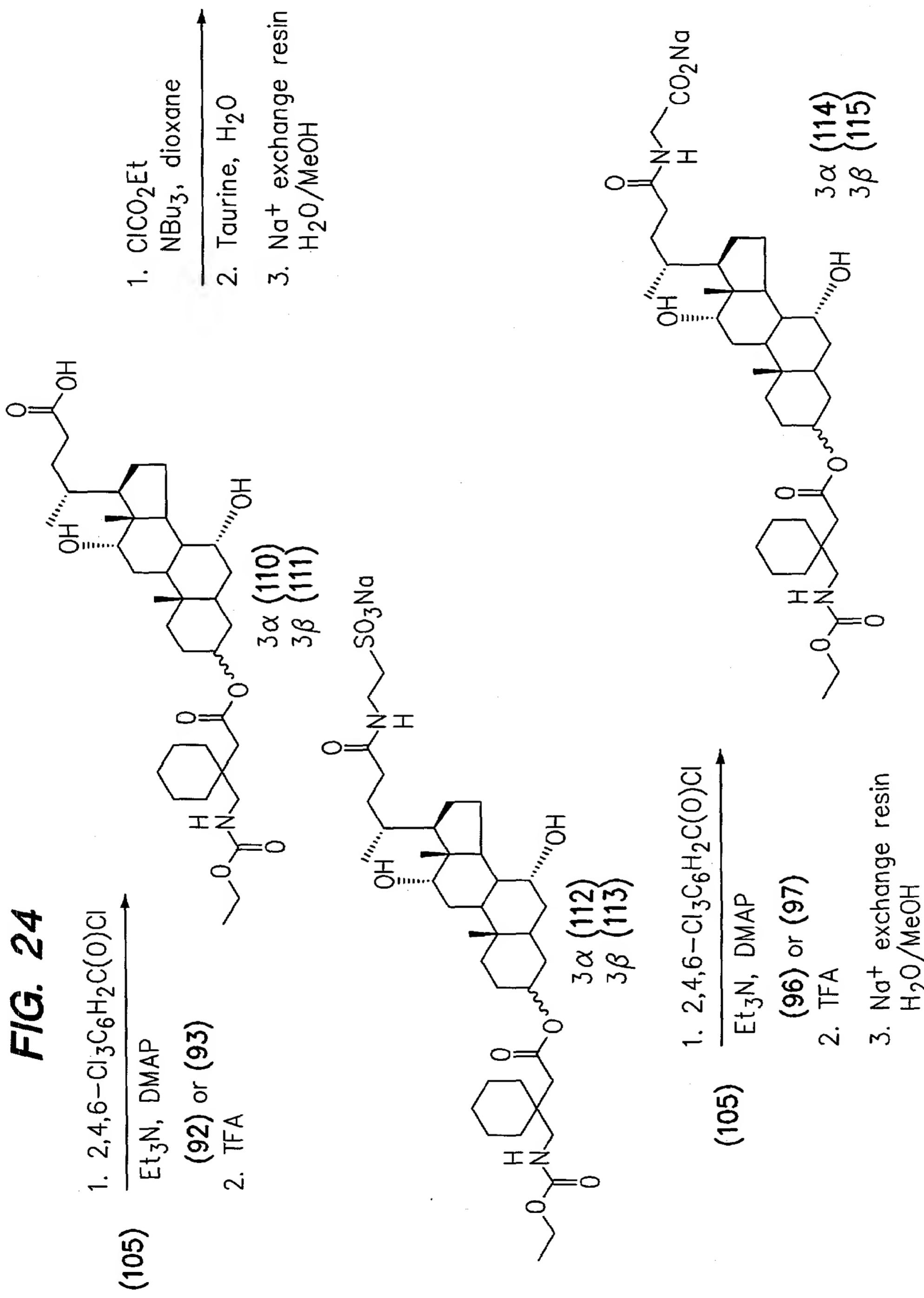
Compounds (92)–(103) prepared following methods described in co-pending application "Bile Acid-Derived Compounds for Enhancing Oral Absorption and Systemic Bioavailability of Drugs" assigned to XenoPort, Inc.

FIG. 23



22/31

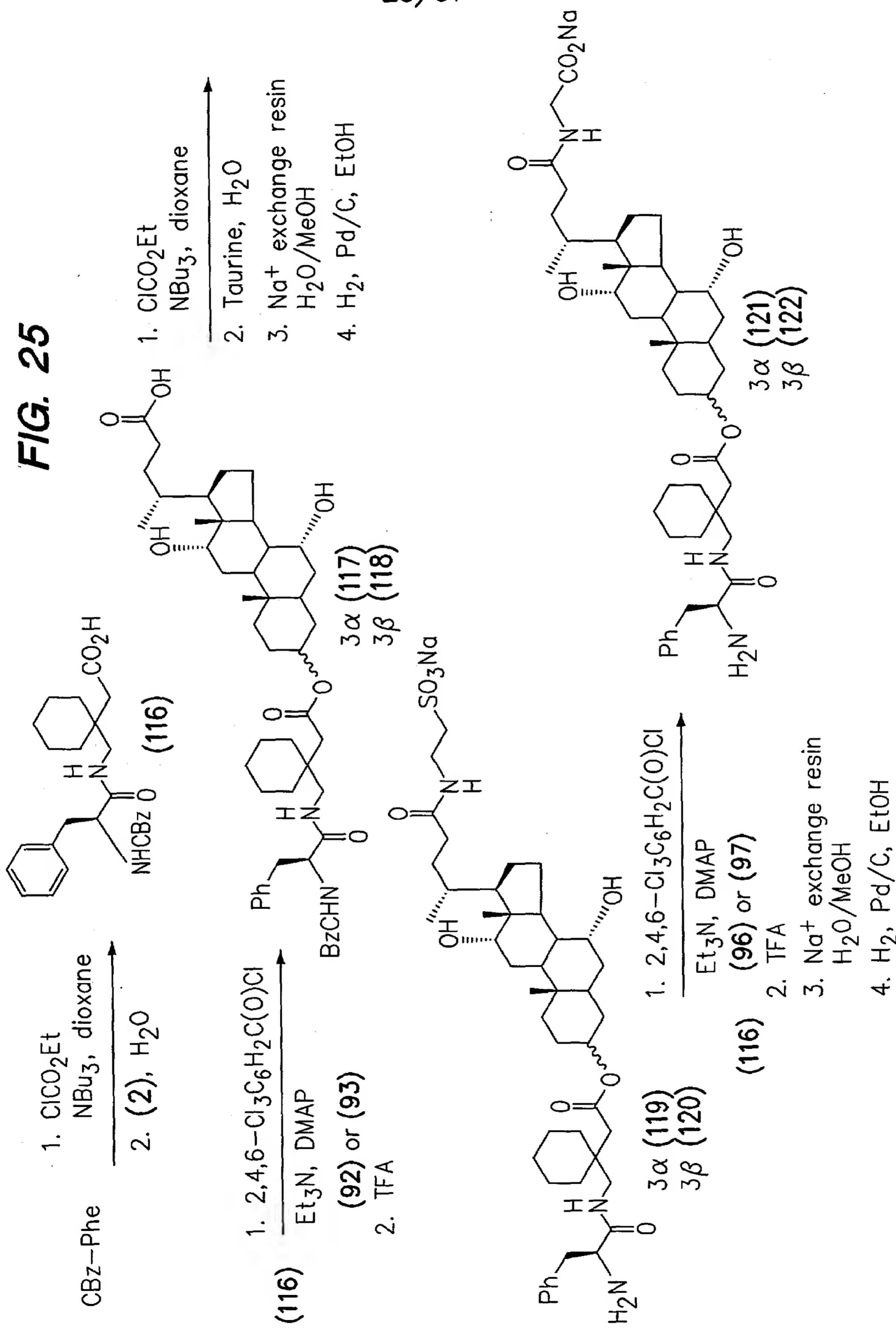
**FIG. 24**



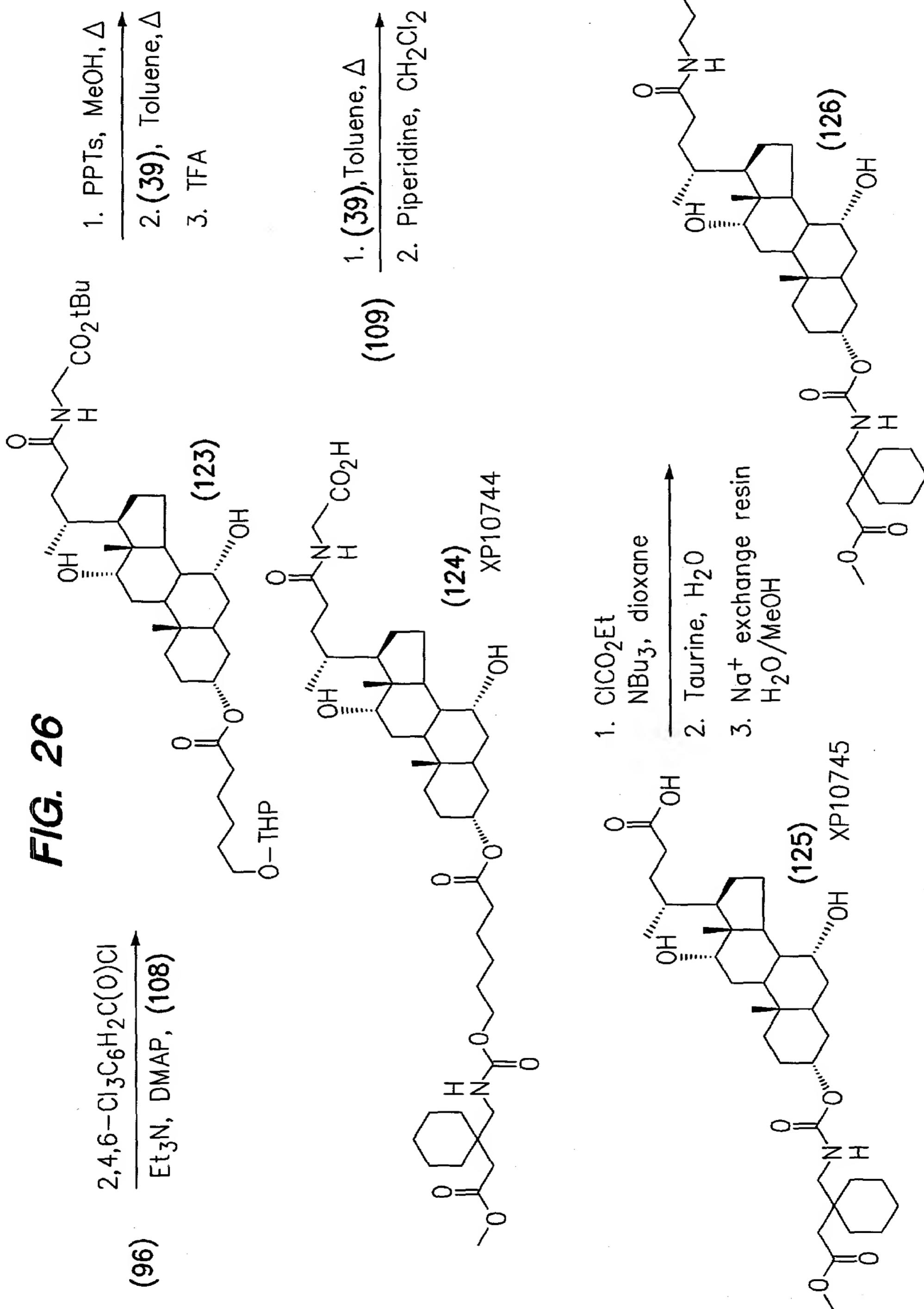
23 OF 31

23/31

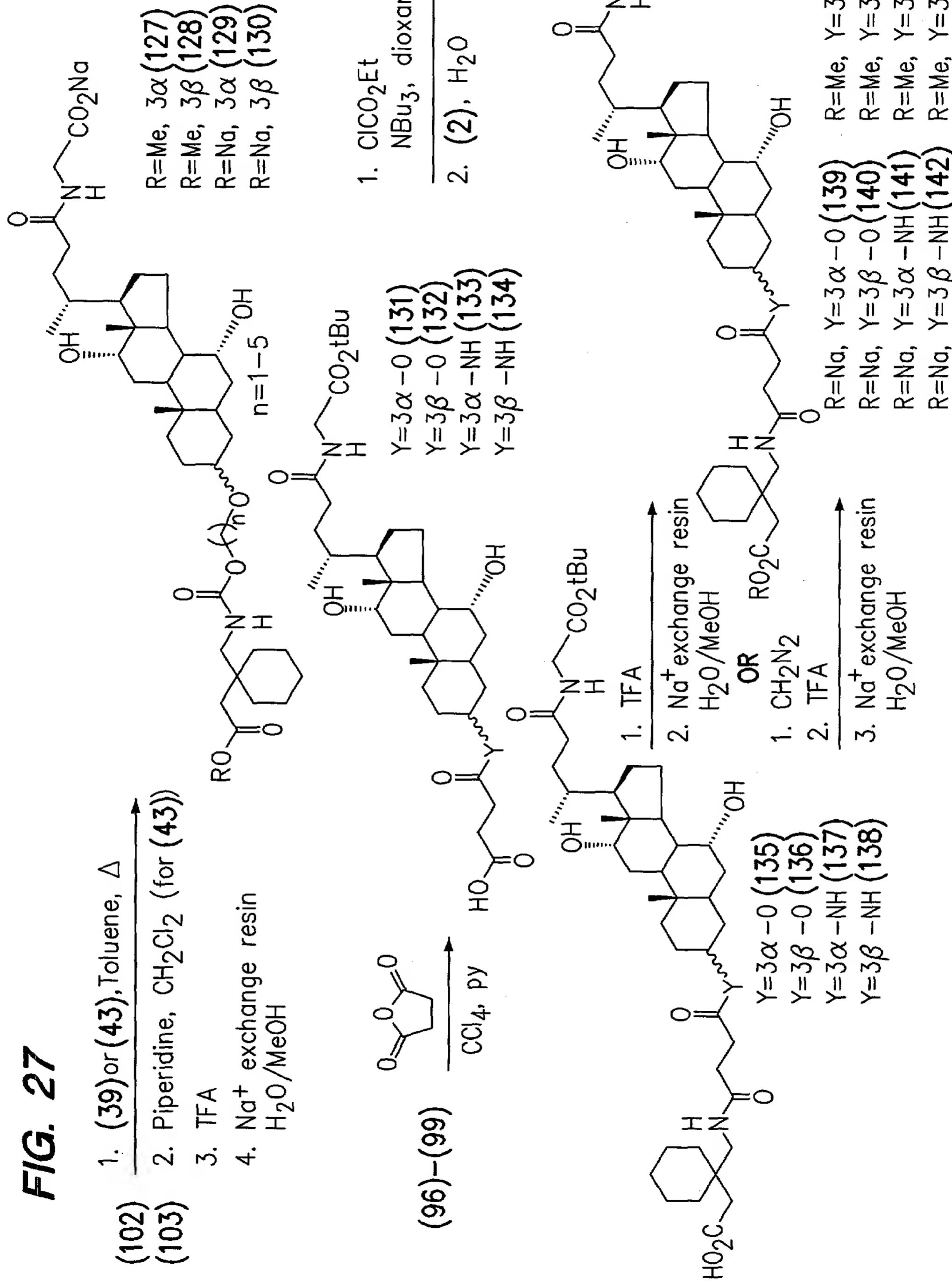
FIG. 25



24/31

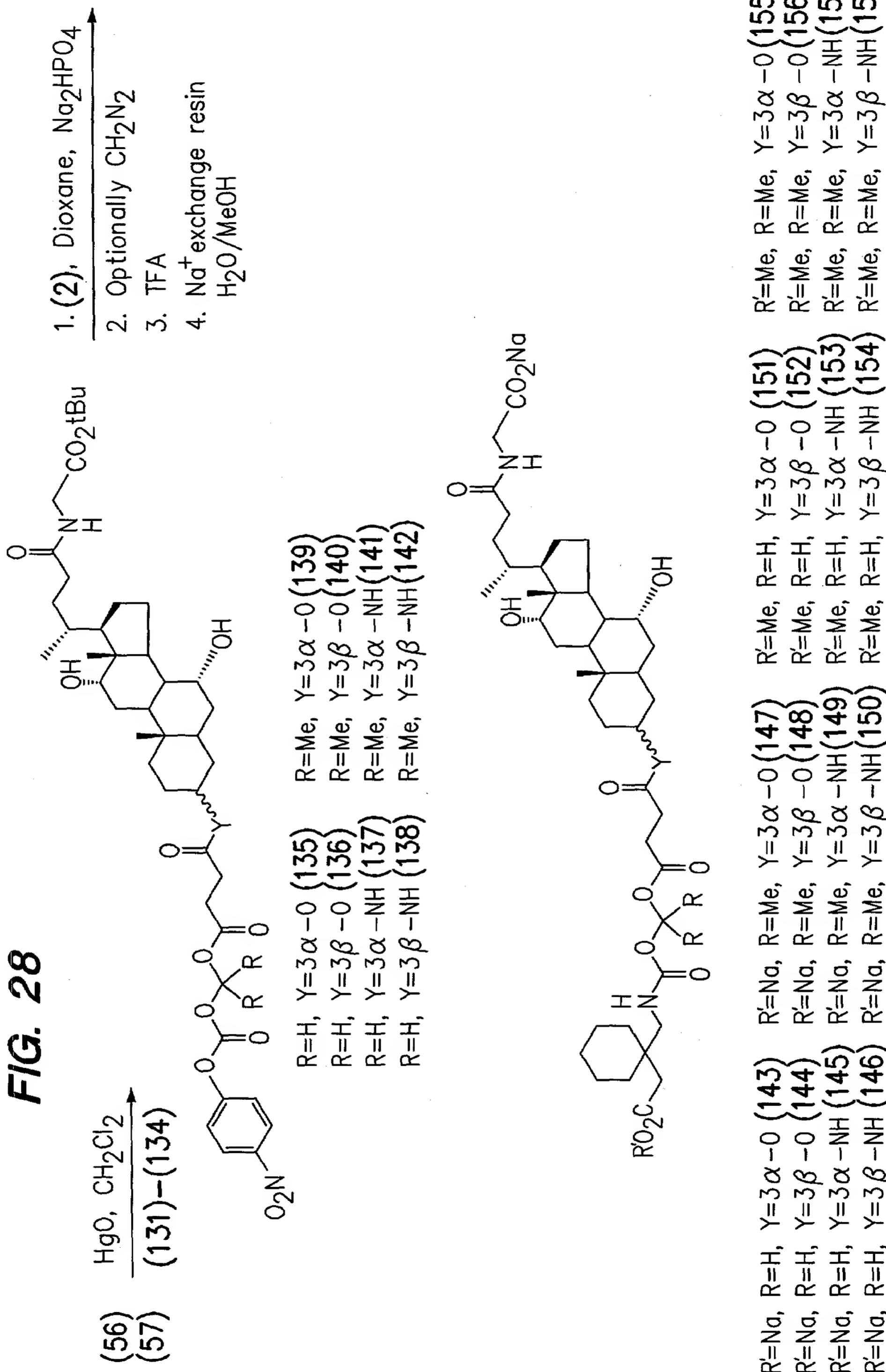


25/31



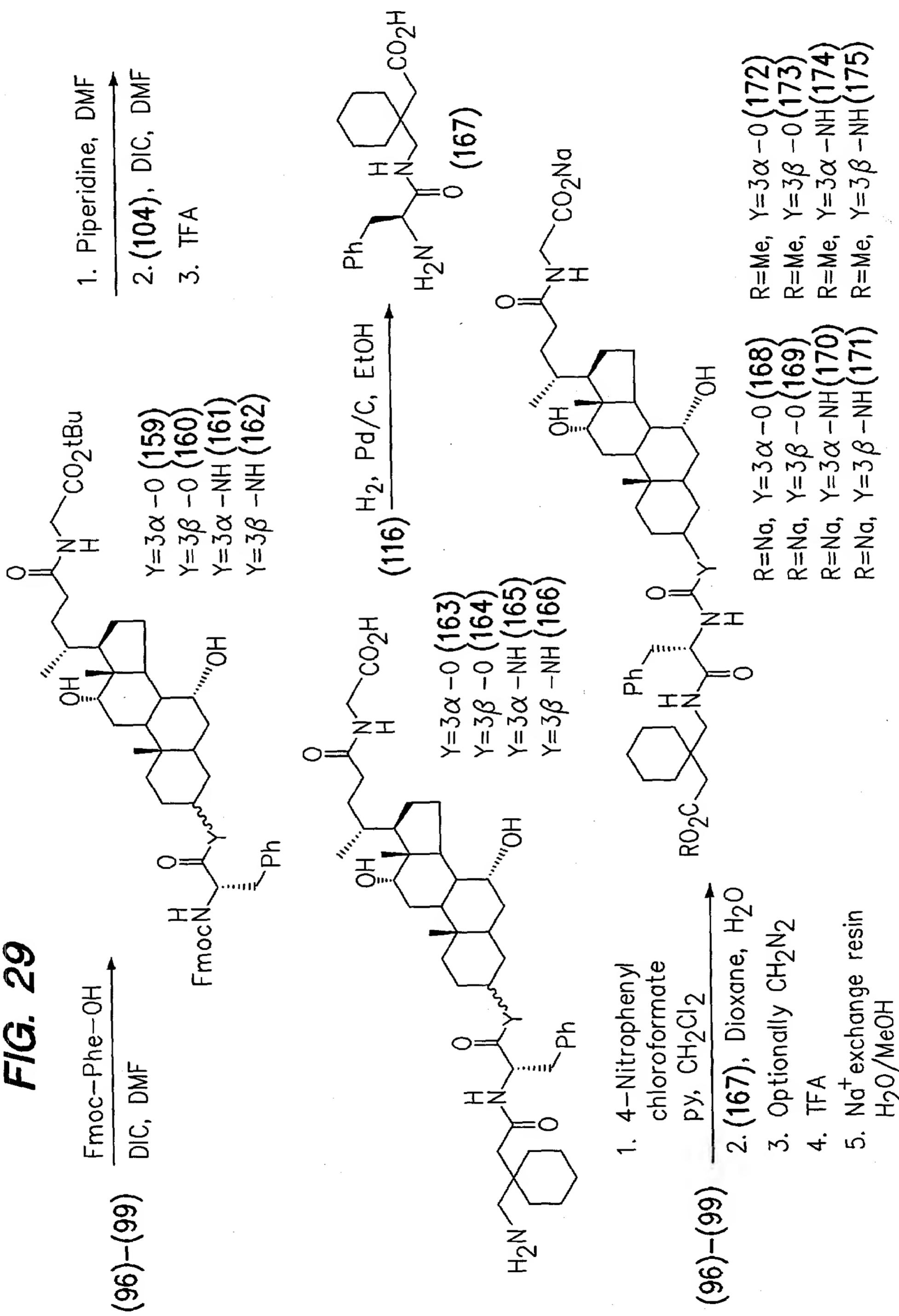
26/31

FIG. 28

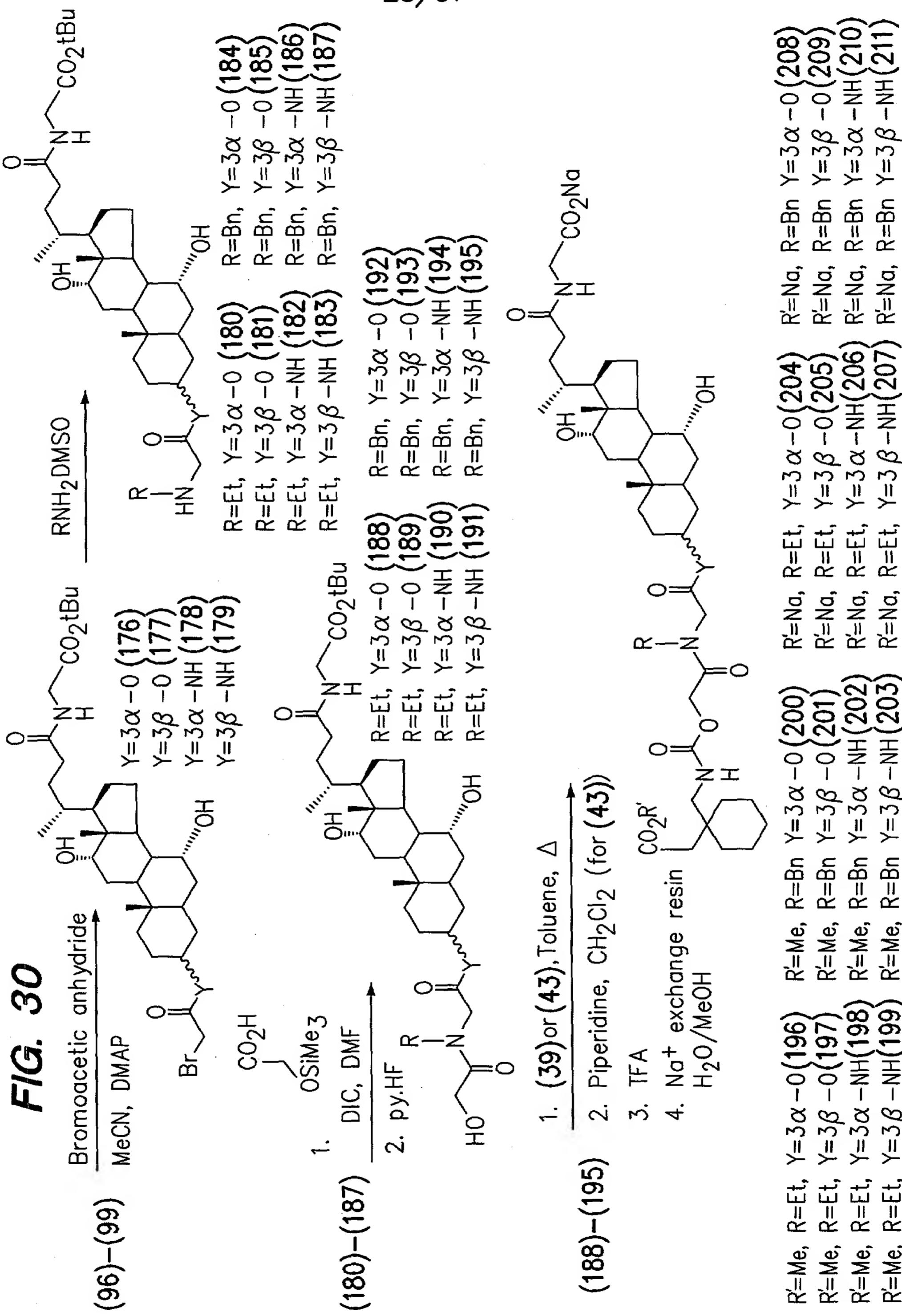


27/31

FIG. 29

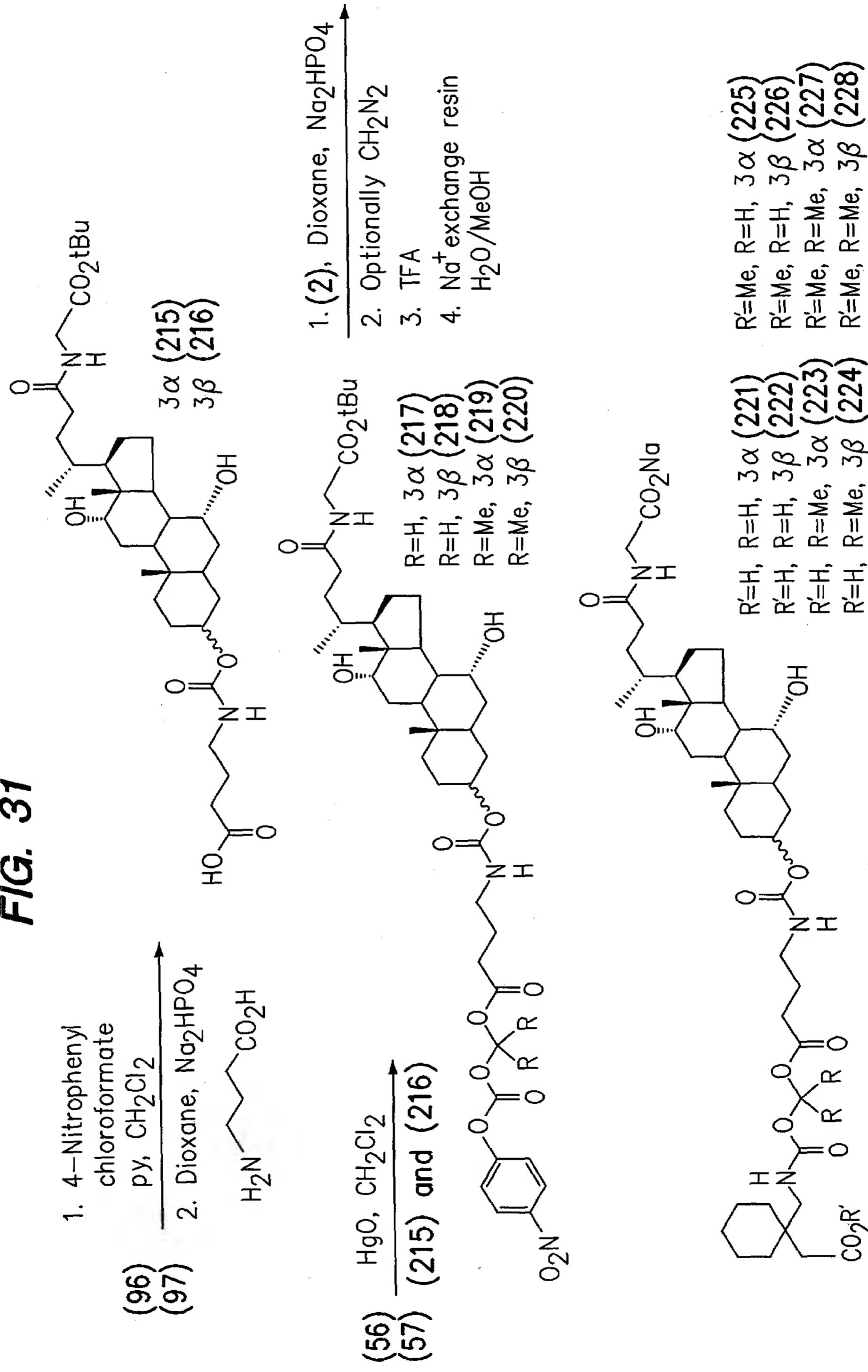


28/31

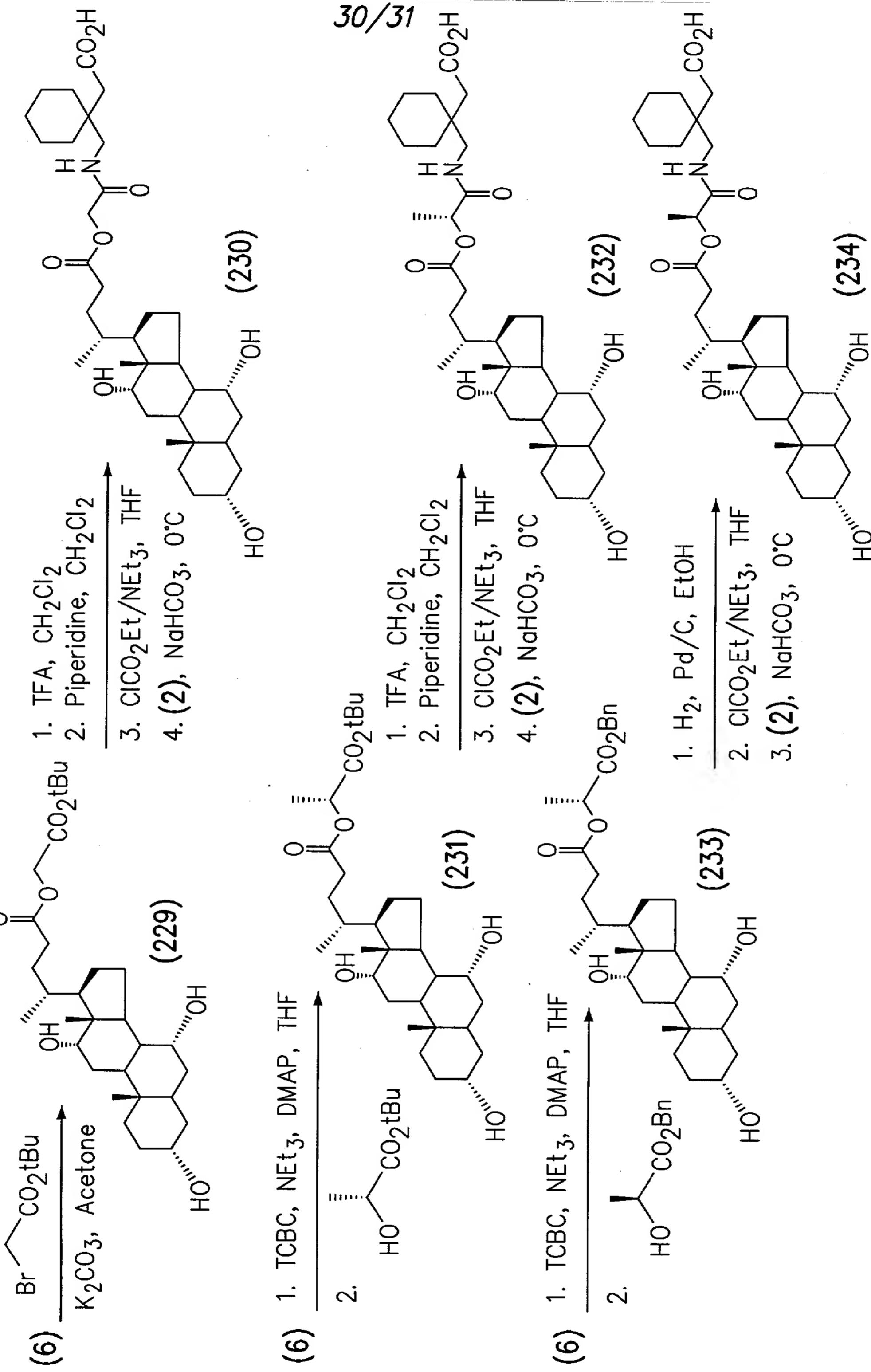


29/31

FIG. 31



**FIG. 32**



31/31

FIG. 33

